NEW METHODS FOR THE SYNTHESIS OF OXYGEN AND NITROGEN CONTAINING HETEROCYCLES

by Matthew Paul Brichacek

NEW METHODS FOR THE SYNTHESIS OF OXYGEN AND NITROGEN CONTAINING HETEROCYCLES

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Matthew Paul Brichacek

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NEW METHODS FOR THE SYNTHESIS OF OXYGEN AND NITROGEN CONTAINING HETEROCYCLES

Matthew Paul Brichacek, Ph. D.

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A single synthetic method rarely is sufficient to provide universal access to a chemical structure class. This realization forces organic chemists to devise and develop new methods. The copper catalyzed ring expansion of vinylaziridines produces nitrogen containing heterocycles commonly found in pharmaceuticals and natural products. This reaction is described from its initial discovery, through optimization, to application. Many substitution patterns and functional groups were tested and the reaction was found to be quite tolerant. By controlling the aziridine and olefin stereochemistry the selective synthesis of either cis or trans 2,5-dihydropyrroles was achieved. Likewise, vinyloxiranes were stereoselectively converted to *cis*- or *trans*-2,5-dihydrofurans. Furthermore, the asymmetric synthesis of 2-substituted-2,5-dihydrofurans was achieved using chirality transfer characteristic of a [1,3]- sigmatropic rearrangement. This method was further tested by completing the total synthesis of natural products goniothalesdiol and varitriol.

BIOGRAPHICAL SKETCH

Matthew Paul Brichacek was born to Rose and Wayne Brichacek on a warm July day of 1983 in Coon Rapids, Minnesota. Matthew was not destined for life in the Twin Cities metropolitan area and while still young, his family moved to the small town of Little Falls. He spent his entire childhood in this community along the Mississippi River and among the waterfalls where the great aviator Charles Lindbergh once roamed. Elementary school produced a student who was more focused on playing hockey than reading, writing, and arithmetic.

When he began his secondary education at the Little Falls Community High School, Matthew became very focused on his studies. He excelled in numerous subjects thanks to the efforts of very talented educators. His love for chemistry had not yet been realized since calculating the pH, energy, and properties of an ideal gas, as well as the significant figures involved, did not excite him. He graduated top of his class in 2001, yet had no idea what career to pursue.

Matthew attended the University of Minnesota Duluth for his undergraduate education. Duluth majestically overlooks Lake Superior where “lake effect snow”, “air conditioning”, and the year-round 4.4^{o}C water are some of his fondest memories. His love for organic chemistry surfaced during his sophomore year. The prevalence of complex molecules around us and the impact these compounds have on our everyday life sparked his interest in synthetic organic chemistry. Professor Robert M. Carlson recruited Matthew to join his laboratory for a summer of challenging research. The putrid smell of sulfur containing compounds however did not scare him away. The mentoring and advice provided by “Dr. Carlson” had a substantial impact on his life.

After graduating from UMD in 2005, Matthew left the safe haven of Minnesota for the east coast and Cornell University. The Finger Lakes region, Cayuga Lake, and Salmon Creek satisfied his love of natural beauty. For his doctoral studies,

he chose to work for assistant professor Jón Njarðarson and the 4th floor of S. T. Olin Laboratory became a second home. After finishing his studies in the summer of 2010, Matthew will continue his scientific career with Paul Hergenrother at the University of Illinois at Urbana-Champaign. He hopes to expand scientifically and yet stay grounded in his love of organic chemistry.

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LIST OF ABBREVIATIONS

Ac	Acetyl
Accy	2-Acetylcyclohexanone
AI	Antarafacial inversion
AIBN	1,1′-Azobis(cyclohexanecarbonitrile)
AR	Antarafacial retention
Bz	Benzoyl
Boc	*tert*-Butyloxycarbonyl
Bn	Benzyl
BTMSA	Bis(trimethylsilyl)acetylene
Bus	*tert*-Butylsulfonyl
CBz	Benzyl carbamate
$Cu(acac)_2$	Copper (II) bisacetylacetonate
$Cu(tfacac)_2$	Copper (II) bistrifluoroacetylacetonate
$Cu(hfacac)_2$	Copper (II) bishexafluoroacetylacetonate
Cy	Cyclohexyl
Dbm	Dibenzoylmethane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
Dibal-H	Diisobutylaluminum hydride
DFT	Density functional theory
DMP	Dimethoxypropane
DMSO	Dimethylsulfoxide
EWG	Electron withdrawing group
Fod	heptafluorobutanoyl)pivaloylmethanate
HPLC	High performance liquid chromatography
Kcal	Kilocalorie

LDA	Lithium diisopropylamide
Lg	Leaving group
LHMDS	Lithium bis(trimethylsilyl)amide
LiDBB	Lithium 4',4'-ditert-butylbiphenylide
mCPBA	3-Chloro-peroxybenzoic acid
Mes	Mesityl
MW	Molecular weight
NBS	N-bromosuccinimide
NCS	N-chlorosuccinimide
ND	Not Determined
NIS	N-iodosuccinimide
NMO	N-Methylmorpholine-N-oxide
Ns	4-Nitrobenzenesulfonyl
Ph	Phenyl
Phth	Phthalimido
PMB	4-Methoxybenzyl
PNB	4-Nitrobenzyl
PPTS	Pyridinium *para*-toluenesulfonate
Py	Pyridine
RT	Room temperature
(S,S)-Ph-box	(S,S)-2,2'-Isopropylidene-bis(4-phenyl-2-oxazoline)
SI	Suprafacial inversion
SR	Suprafacial retention
TBAF	Tetra-N-butylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl

Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TMEDA	*N*,*N*,*N*',*N*'-Tetramethylethylenediamine
TMS	Trimethylsilyl
TMSI	Trimethylsilyliodide
Ts	Toluenesulfonyl

Chapter 1

Introduction

1.1 Heterocycle Containing Natural Products, and Pharmaceuticals

The field of organic synthesis has experienced tremendous growth over the last century enabling scientists to construct increasingly complex molecules. This growth has been realized because of the intricate interplay between synthetic methodology and total synthesis. Whereby, the discovery and development of new reactions enables more efficient, shorter syntheses. Alternatively, the pursuit of natural products offers an opportunity to test methodologies and discover new ones. Table 1.1 summarizes the Nobel Prizes received in the area of organic synthesis and demonstrates that scientists

Table 1.1: Nobel Prizes in Organic Synthesis (1901-2010)

Year	Recipient	Prize Motivation	Specialty
1902	Emil Fischer	Sugar and purine syntheses	Total Synthesis
1905	Adolf von Baeyer	Organic dyes and hydroaromatic compounds	Total Synthesis
1910	Otto Wallach	Alicyclic compounds	Total Synthesis
1912	Victor Grignard	Grignard reagents	Methodology
	Paul Sabatier	Metal catalyzed hydrogenations	Methodology
1930	Hans Fischer	Haemin	Total Synthesis
1937	Norman Haworth	Carbohydrates and vitamin C	Total Synthesis
	Paul Karrer	Carotenoids, flavins and vitamins A and B2	Total Synthesis
1938	Richard Kuhn	Carotenoids and vitamins	Total Synthesis
1939	Adolf Butenandt	Sex hormones	Total Synthesis
	Leopold Ruzicka	Polymethylenes and higher terpenes	Total Synthesis
1947	Sir Robert Robinson	Alkaloids	Total Synthesis
1950	Otto Diels, Kurt Alder	Diels-Alder reaction	Methodology
1955	Vincent du Vigneaud	Polypeptide hormones and sulfur compounds	Total Synthesis
1957	Lord Alexander Todd	Nucleotides and nucleotide co-enzymes	Total Synthesis
1965	Robert B. Woodward	Art of organic synthesis	Total Synthesis
1969	Derek H. R. Barton, Odd Hassel	Conformations of molecules	Structure and Theory
1975	John Cornforth, Vladimir Prelog	Stereochemistry of molecules	Structure and Theory
1979	Herbert C. Brown	Boron containing compounds	Methodology
	Georg Wittig	Phosphorus containing compounds	Methodology
1981	Kenichi Fukui, Roald Hoffmann	Course of chemical reactions	Structure and Theory
1984	R. Bruce Merrifield	Chemical synthesis on a solid matrix	Methodology
1990	Elias J. Corey	Theory and methodology of organic synthesis	Methodology Total Synthesis
1994	George A. Olah	Carbocation chemistry	Structure and Theory
2001	William S. Knowles, Ryoji Noyori	Asymmetric hydrogenation	Methodology
	K. Barry Sharpless	Asymmetric oxidation reactions	Methodology
2005	Robert Grubbs, Richard Schrock, Yves Chauvin	Metathesis	Methodology

in both areas of expertise have been recognized for their advancements.[1] In the realm of synthetic methodology one can argue that the discovery of a truly "new" synthetic method is quite difficult. Many new reactions are actually new protocols of existing reactions or creating a cascade of known reactivity.[2] However, improvements of these types can have profound impact allowing broader substrate scope, diastereocontrol, or asymmetric variants. Therefore synthetic methodology and total synthesis will continue to grow in technique and art for the foreseeable future.

Representative natural products that are considered "classics" in our discipline are shown in Figure 1.1.[3] The synthesis of these molecules represented a significant advancement in the field of total synthesis at the time of their completion. Common to a plethora of natural products are heterocycles and more specifically 5-membered heterocyclic rings containing oxygen, nitrogen, and sulfur. These rings can be aromatic (furan, pyrrole, thiophene), partially reduced, or saturated (tetrahydrofuran, pyrrolidine, tetrahydrothiophene). Many diverse and creative approaches to construct these motifs have been developed, but no single method provides ready access to this entire substrate class.

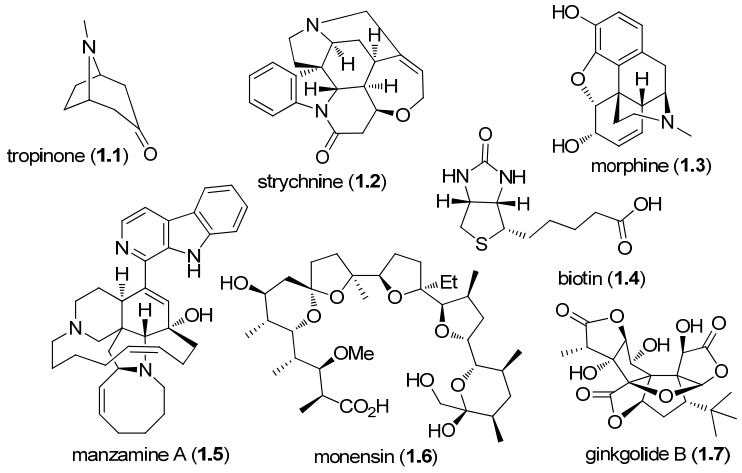


Figure 1.1: Classic Natural Product Architectures with 5-Membered Heterocycles

Pharmaceuticals also contain 5-membered heterocycles and several of the top selling drugs in 2008 that contain this motif are shown in Figure 1.2. The synthesis of pharmaceuticals is of equal if not superior importance to that of natural products. Although the structural complexity is often lower, the necessity for efficiency, enantiopurity, and scaleability can make the synthesis of pharmaceuticals more challenging. These requirements mandate an influx of new methods and protocols for the synthesis of approved compounds, but also access to new architectures for drug discovery.

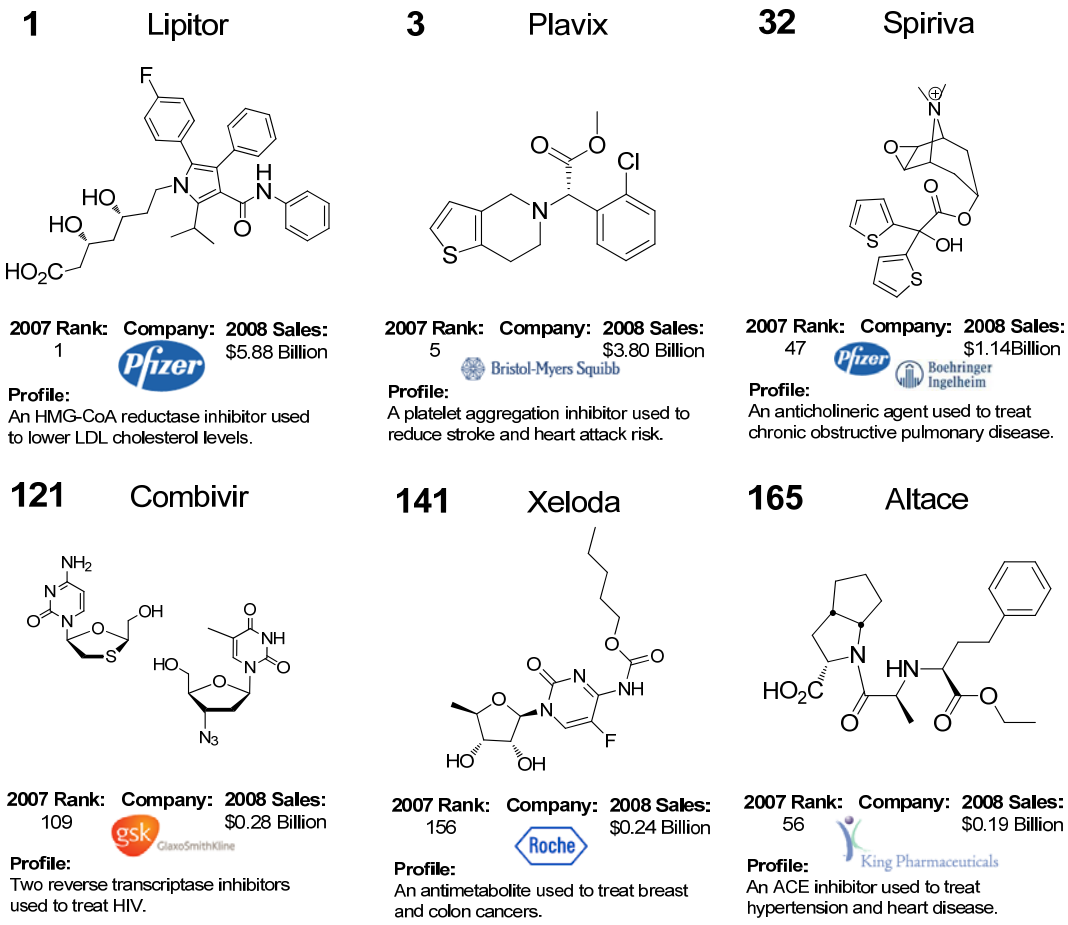


Figure 1.2: Important Pharmaceuticals with 5-Membered Heterocycles

Lipinski's rules (Lipinski's Rule of Five)[4] are used to evaluate drug likeness, but these rules can be expanded by analysis of the top selling pharmaceuticals over the last few years. Some of these startling trends and statistics are shown in Table 1.2. The top 200 brand-name and generic pharmaceuticals by sales are comprised predominantly of small organic molecules (~407 g/mol) and a few inorganic, polymer, and biological molecules. These small organic molecules on average have 21 carbon, 27 hydrogen, 4 oxygen, and 3 nitrogen atoms. Also, these pharmaceuticals sometimes contain sulfur, fluorine, chlorine, and phosphorous, but rarely any other elements. Further analysis reveals that most of these molecules are cyclic and in particular the ring contains a heteroatom such as nitrogen oxygen, or sulfur. These vast generalizations to the structure of the top selling pharmaceuticals allows one to conclude that small heterocyclic structures are prevalent in the pharmaceutical space explored to date.

Table 1.2: Characteristics of the Top 200 Selling Pharmaceuticals

Year	Type	Avg. MW (g/mol)	Average Composition						Organic Molecules		Biological	Inorganic	Polymers
			C	H	O	N	S	F	Cyclic	Heterocyclic			
2006	Generic	376.4	19.1	24.5	4.0	2.3	0.3	0.1	190	134	1	3	2
2006	Brand-Name	441.8	22.9	29.1	4.2	2.7	0.4	0.3	172	130	18	1	3
2007	Generic	371.1	18.9	24.2	3.8	2.4	0.3	0.1	188	127	2	4	2
2007	Brand-Name	439.4	23.0	29.0	4.0	2.8	0.4	0.3	171	134	18	1	4
2008	Generic	374.6	19.1	24.7	3.9	2.4	0.3	0.1	185	128	3	3	0
2008	Brand-Name	436.8	22.8	28.9	4.0	2.8	0.3	0.4	168	128	17	2	4

More in-depth analysis of the heterocycles present in pharmaceuticals reveals several trends displayed in Table 1.3. The presence of each heterocycle has been quantified with respect to launched drugs, ones in clinical trials, and all those which have been tested for biological activity and deposited in the MDL drug database.[5] The presence of small rings (3,4), regardless of the heteroatom, are very rare in pharmaceuticals except for the plethora of β-lactams. Next, five-membered rings, not surprisingly, are quite common for nitrogen and oxygen while sulfur containing heterocycles make their only contribution to launched drugs here. Lastly, nitrogen

overwhelms oxygen with respect to 6-membered rings. From these trends we conclude that nitrogen and oxygen containing 5- and 6- membered heterocycles are common motifs found in pharmaceuticals of a wide variety of biological modes of action. Therefore, new methods that facilitate the construction of these motifs will enable the synthesis of new structures yet to be tested or enable the more efficient synthesis of existing structures.

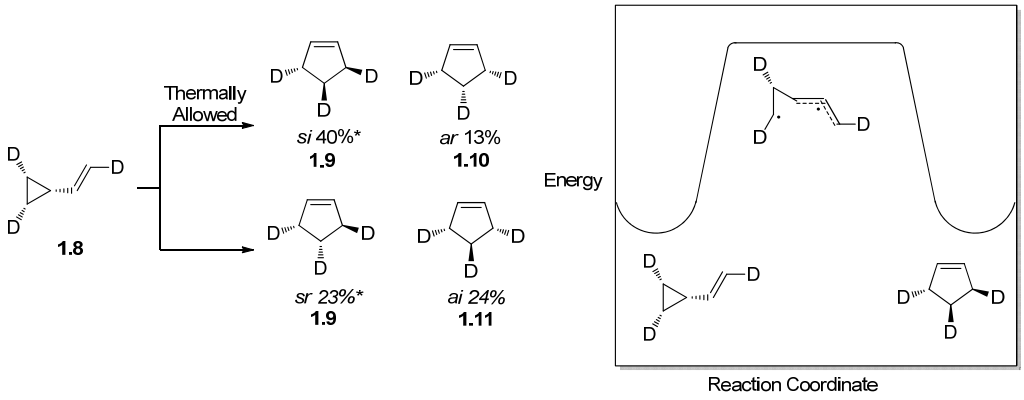
Table 1.3: Analysis of Heterocycles Found in Pharmaceuticals

Heterocycle	Launched	Clinical Trials	All
	2	9	241
	69	64	5415
	220	614	38298
	327	916	66599
	12	86	1045
	3	18	682
	77	438	10695
	85	153	8916
	0	0	3
	0	0	19
	34	101	9855
	0	9	313

1.2 [1,3]-Sigmatropic Rearrangements

Sigmatropic rearrangements have proved to be a valuable tool for organic chemists in the synthesis of complex molecules. The value of these transformations is based on the precise regio- and stereo-control offered by many pericyclic reactions.[6] The [1,3] sigmatropic rearrangement, in particular the isomerization of vinylcyclopropanes to cyclopentenes, has been utilized numerous times in the

synthesis of natural products.[7] The first vinylcyclopropane isomerization to a cyclopentene was observed by Neureiter in 1959 with 1,1-dichloro-2-vinylcyclopropane (**1.11h**).[8] This reaction prompted thorough study and discussion of the parent, unbiased vinylcyclopropane rearrangement. Utilizing a wide variety of physical organic experiments and calculations the mechanism is best explained in terms of a concerted rearrangement that has a biradical like transition state (Scheme 1.1). The transition state is located on a very flat surface which leads to several products arising from the orbital symmetry allowed (suprafacial inversion, antarafacial retention) and the forbidden (suprafacial retention, antarafacial inversion) pathways. The energy of activation was determined to be 52 kcal/mol using several different methods.

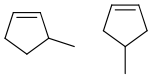
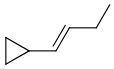
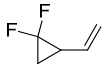
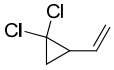
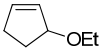
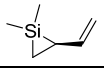


Scheme 1.1: Stereochemical Outcome of Vinylcyclopropane Rearrangement

Selected examples of the perturbation of the vinylcyclopropane rearrangement are displayed in Table 1.4. The changes in reactivity are readily explained by stabilization of the biradical like transition state. It is clear that adding substituents to the parent systems dramatically alters the energetics and stereochemical outcome. In light of this, it is not surprising that involving a heteroatom in the strained ring (oxirane, thiirane, aziridine, phosphirane, silyrene, etc.) will result in fundamentally different reactivity. For example the thermal rearrangement of the vinylphosphirane

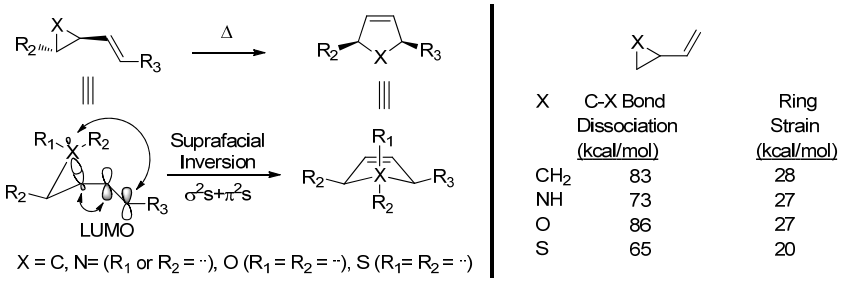
(**1.11k, 1.11l**) to the phospholene **1.12k, 1.12l**) was studied and found to most likely proceed by a biradical. The reaction can be catalyzed by transition metals and the energies of activation for both the catalyzed and non-catalyzed processes were calculated. The large effect of a Lewis acid catalyst bodes well for utilizing transition metals to catalyze variants of this rearrangement with lone pairs. The vinylsilyrene (**1.11m**) was studied and the barrier to rearrangement was prohibitively high such that extrusion and 1,4 insertion was found to be a more accessible pathway. Together these results show that future attempts to ring expand strained rings will be challenging because of the high activation energy and the surface around the transition state.

Table: 1.4: [1,3]-Rearrangement of Vinylcyclopropanes

	Vinylcyclopropane (**1.11**)	Product (**1.12**)	Temperature (°C)	Energy of Activation (kcal/mol)
a[9]			325-390	52
b[10]			270-330	45
c[10]			313-357	49
d[10]			332-386	51
e[10]			332-373	50
f[10]			325-368	51
g[11]			195-224	40
h[12]			200-300	ND
i[13]			273-323	45
j[14]			220-280	39
k[15]			150	37* (21)**
l[15]			150	29* (22)**
m[16]			500-650	42*

ND = Not Determined, * = Calculated Energy, ** = $Cr(CO)_5$ catalyzed Calculated Energy

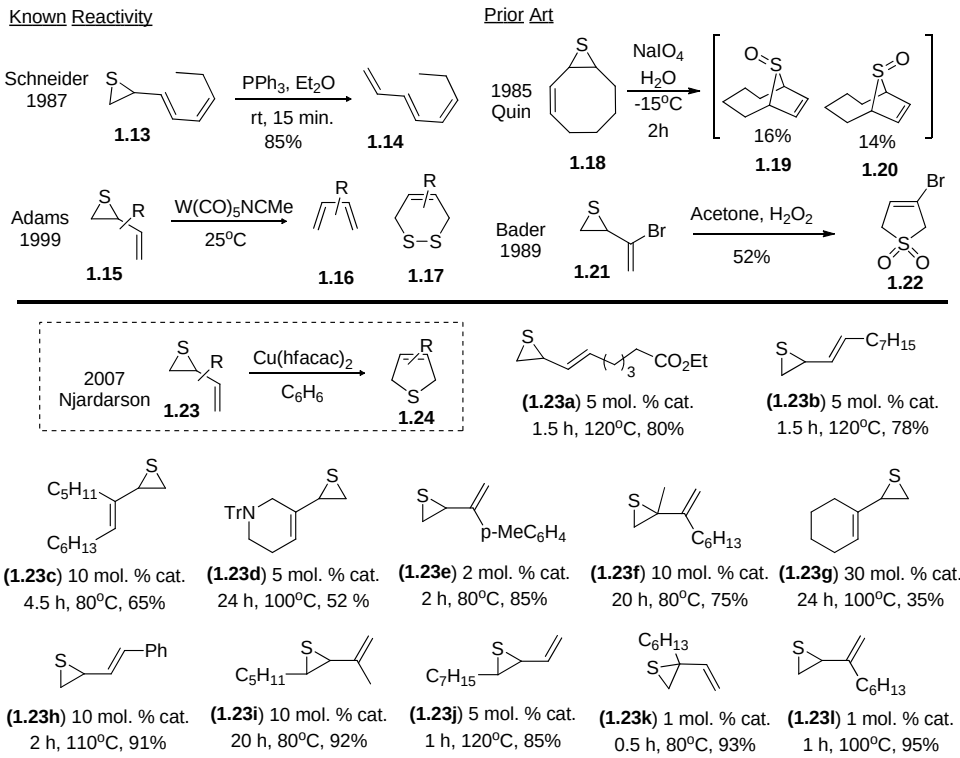
The development of a [1,3] rearrangement of a strained heterocycle would be of great value to synthetic chemists. Scheme 1.2 shows the orbital symmetry allowed pathway for a true, concerted rearrangement. Analysis of the bond dissociation energies and ring strain suggest that this reaction should be feasible. A thorough study of the literature for [1,3] rearrangements of vinyl-thiiranes, -oxiranes, and -aziridines teaches us that this is non-trivial.



X	C-X Bond Dissociation (kcal/mol)	Ring Strain (kcal/mol)
CH_2	83	28
NH	73	27
O	86	27
S	65	20

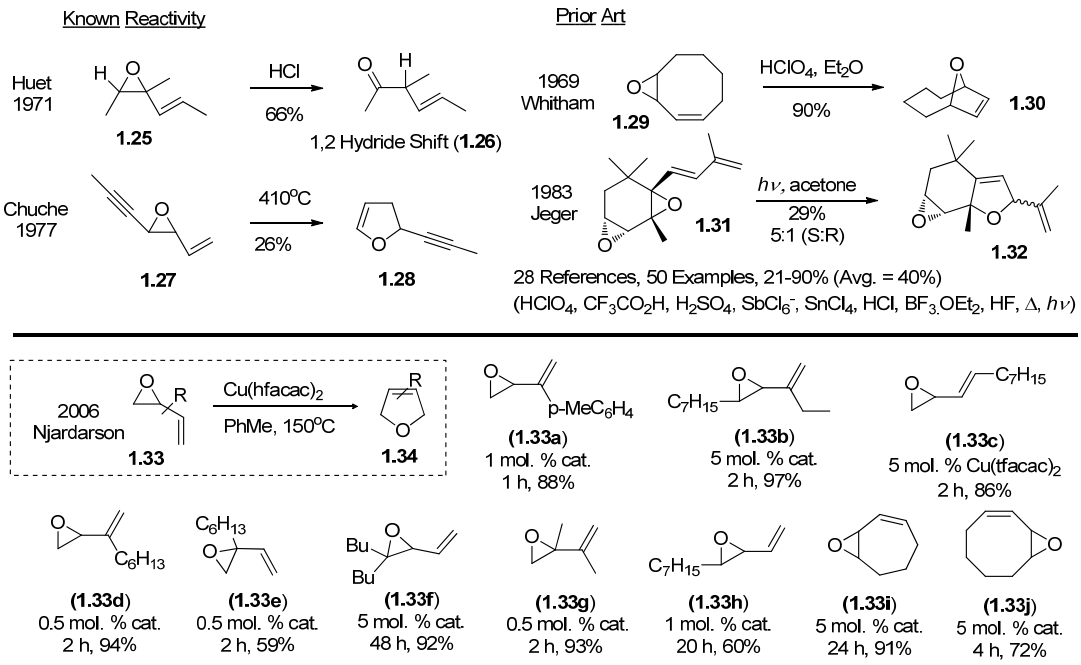
Scheme 1.2: Stereochemical Rationale and Energetics for [1,3] Sigmatropic Rearrangement of Various Three-Membered Heterocycles

The first publication of a formal [1,3] rearrangement of a vinylthiirane was not performed until Quin in 1985 (Scheme 1.3).[17] The oxidation of the mono-thiirane of cyclooctadiene results in the isolation of both sulfoxide diastereomers of the [4.2.1] bicycle (**1.19, 1.20**) in modest yield. Likewise, attempted oxidation of a vinylthiirane by Bader produced sulfolene **1.22**.[18] The true ring expansion of a vinylthiirane was not realized until 2007 by Njardarson et. al.[19] Vinylthiiranes (**1.23**) with varying substitution patterns and functional groups could be treated with copper (II) bishexafluoroacetylacetonate ($Cu(hfacac)_2$) and the dihydrothiophenes (**1.24**) were isolated in good yield. This catalytic reaction, with appropriate choice of temperature and catalyst loading, was able to overcome the extrusion of sulfur which was known inherent reactivity of vinylthiiranes.[20,21]



Scheme 1.3: Ring Expansion of Vinylthiiranes

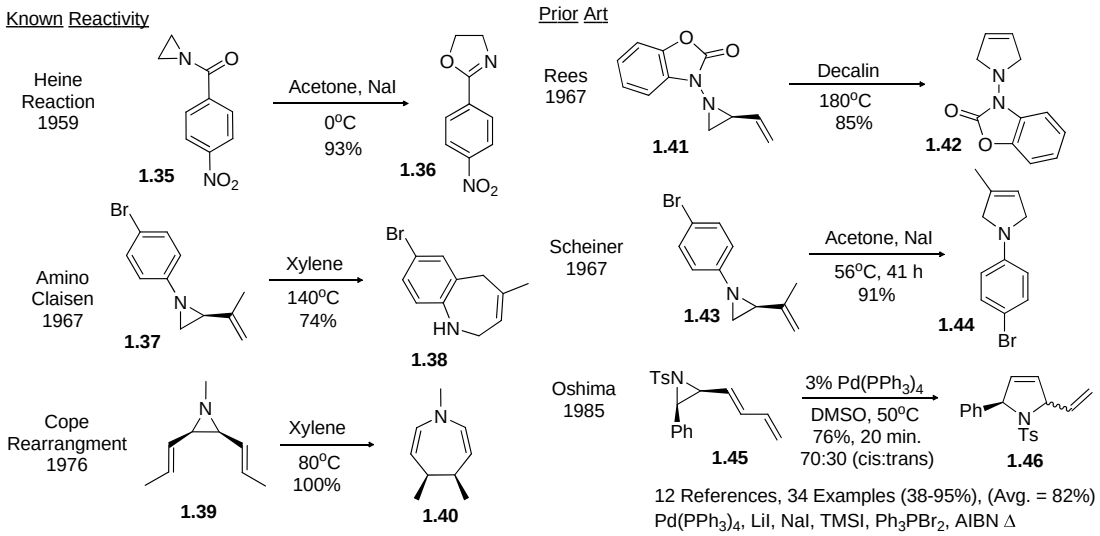
Garnering significant more attention is the ring expansion of vinyloxiranes (Scheme 1.4). The acid catalyzed expansion by Whitam in 1969 represents the first example and one of the highest yields reported.[22] The results of Jeger[23] are representative of Bronsted/Lewis acid catalyzed ring expansion of vinyloxiranes despite the use the photochemical conditions in this example. Low yield and no control of the stereochemistry is observed, but more limiting is the [1,2] hydride shift that is often the major product when a hydrogen is present adjacent to the vinyl group on the oxirane.[24] These shortcomings were present until 2006 when Njardarson et. al. published a copper (II) bishexafluoroacetylacetonate catalyzed ring expansion of vinyloxiranes.[25] Once again the metal catalyzed reaction was able to overcome known reactivity of the vinyloxirane.[26,27]



Scheme 1.4: Ring Expansion of Vinyloxiranes

The formal [1,3] rearrangement of a vinylaziridine to a 3-pyrroline was first observed by Rees and Scheiner independently in 1967 (Scheme 1.5).[28,29] The rearrangement can be performed using thermal conditions when appropriate groups are present on the nitrogen of the aziridine or done in an S_N2' fashion with soft nucleophiles. In each case, severe limitations were observed with respect to functional group compatibility and the substitution patterns tolerated. A major advance was made by Oshima who found the process could be catalyzed by Pd^0, but only for dienylaziridines.[30] Also, the stereochemical outcome resulted in what appears to be a thermodynamic mixtures of products. This technology facilitated the synthesis of numerous pyrrolines, but a general method was still lacking.[31] The typical reactivity that was known for vinylaziridines with carbonyl groups on the nitrogen was to undergo the Heine reaction to form an oxazolidine.[32] Secondly, the thermolysis of aryl vinylaziridines is known to produce azepines by an amino-Claisen rearrangement. Lastly, divinylaziridines were shown to undergo strain assisted Cope rearrangements

also to azepines.[33] These competing thermal reactions may limit the groups present on the nitrogen in the [1,3] rearrangement. We hope to achieve another milestone in the history of this process by facilitating the reaction with broad functional group compatibility, tolerance of various substitution patterns, and control of stereochemistry.



Scheme 1.5: Ring Expansion of Vinylaziridines

1.3 Synthesis of Dihydrofurans, Dihydrothiophenes, and Dihydropyrroles

It is clear that the need for operationally simple, atom-efficient methods with as broad substrate scope as possible will always be great. It is important to emphasize that one type of chemical transformation can rarely provide universal access to all substrate permutations of a given class. Efforts should be devoted to developing a series of complementary practical synthetic methods that together can provide access to every member of a given substrate class. Such practical new synthetic methods can have a significant impact since a large number of research areas rely on building new molecular architecture either for fundamental or industrial applications

Five membered heterocycles are essential building blocks that are frequently used in the pharmaceutical and commodity chemical industry. For example, more than 65% of pharmaceuticals contain at least one heterocyclic fragment. Our group has dedicated substantial efforts to developing a useful synthetic approach that can afford access to a broad range of 2,5-dihydro- furan, thiophene, and pyrrole products. These products are very attractive building blocks *en route* to natural products, pharmaceuticals, materials, and commodity chemicals. The 3,4-unsaturation of these heterocycles is a particularly attractive feature as it enables straightforward access to reduced, oxidized, and further functionalized members of these three important structural families. Members of the furan family can be found in thousands of natural products, bulk commodity chemicals, and pharmaceutical agents.[34] Thiophenes are used for a number of practical applications such as pharmaceuticals and materials.[35] A significant number of marketed and approved drugs contain a pyrrolidine core, with the most commonly employed derivatives being proline or azabicyclics.[36] The tropane core ([3.2.1]-azabicyclic), for example, is the structural backbone of many very successful therapeutics.[37]

The eight distinct 2,5-dihydro- furan, thiophene, and pyrrole retrosynthetic approaches are highlighted in Figure 1.3. In this discussion we have chosen not to cover any synthetic methods that form either fused aromatic products or those that are sp^2-hybridized at either the 2- or 5-positions, which also excludes lactones, lactams, and such derivatives. Finally, the only methods discussed are considered "general" in that they allow access to all three heterocycle classes. Although this stipulation seems very restrictive only a few notable methods are not discussed. Each synthetic approach is discussed in the following sections. A brief outline is followed by reaction comments and literature examples highlighting their strengths. Whenever possible we have chosen natural product examples.

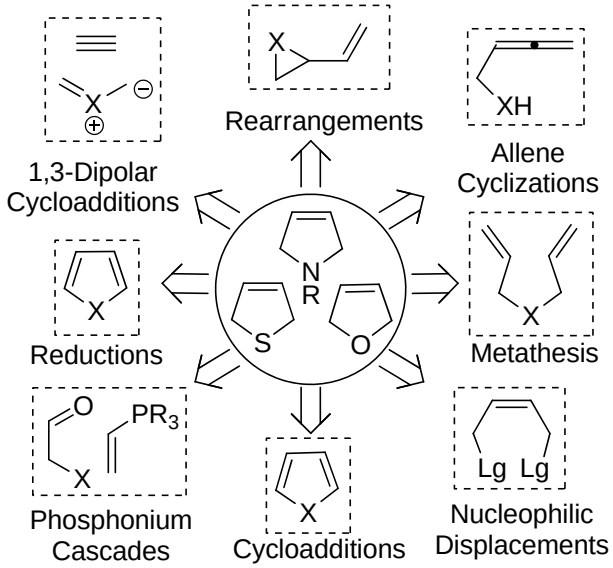
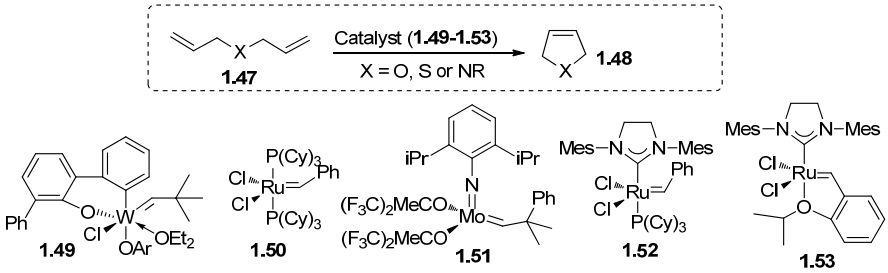


Figure 1.3: Eight Retrosynthetic Approaches for 2,5-Dihydro- Furans, Thiophenes, and Pyrroles

1.3.1 Ring Closing Metathesis

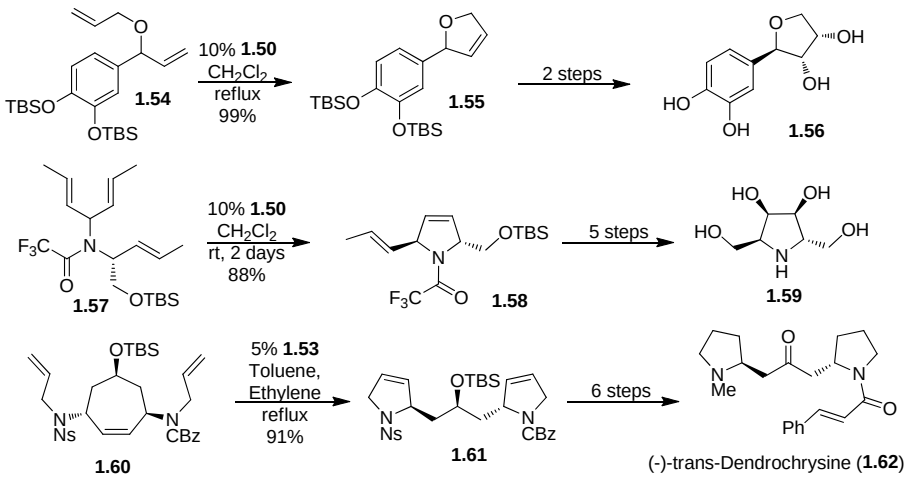
Metathesis reactions, and ring closing metathesis (RCM) in particular, have in the last fifteen years revolutionized how organic chemists design and assemble molecules.[38] Not surprisingly this new synthetic approach was quickly applied to the construction of 2,5-dihydro- furan, thiophene, and pyrrole products (Scheme 1.6, **1.48**). Early efforts utilized tungsten (**1.49**),[39] ruthenium, and molybdenum catalysts, with Grubbs (**1.50**)[40] and Schrock (**1.51**)[41] catalysts being featured most prominently. In accessing simple heterocyclic products the primary challenges that were encountered were catalyst inhibition by sulfide[42] and free amine substrates[43] as well as unwanted olefin isomerization of dihydrofuran products.[44] Many of these challenges have since been overcome. Second generation ruthenium catalysts such as **1.52**[45] and **1.53**[46] have led the way because of their attractive air stability and functional group compatibility. For example, by utilizing suitably protected diallylamines, 3-pyrrolines can now be readily accessed.[47] Diallyl sulfides are now manageable substrates[48] although challenges still exist and in many cases sulfones[49] are used as substitutes.

The dihydrofuran olefin isomerization challenge has been addressed by using a benzoquinone additive.[50] Tetrasubstituted and strained bicyclic substrates continue to be very challenging for ring closing metathesis, although recent new catalyst developments indicate that the tetrasubstituted products will soon be more accessible.[51] From a retrosynthetic point of view, metathesis is less appealing for 2,5-substituted substrates as synthesis of the requisite starting materials can be challenging at times. Additionally, the fact that a large amount of solvent is usually needed coupled with high catalyst cost, non-trivial catalyst removal, and toxicity challenges often make the scale-up less attractive.



Scheme 1.6: Synthesis of 2,5-Dihydro- Furans, Thiophenes, and Pyrroles Using Metathesis

This new synthetic approach has been utilized for natural product synthesis with great success (Scheme 1.7). Most examples reported to date have employed this strategy to access 3-pyrrolines *en route* to a target natural product. Lack of dihydro- or tetrahydrothiophene containing natural products probably accounts for the fact that no such 2,5-dihydrothiophene examples exist. Aryl furan natural product **1.56** was easily assembled from benzylic allyl ether **1.54** using Grubbs first generation catalyst.[52] Blechert has taken advantage of ring closing metathesis to access azasugar **1.59**[53] and the natural product (-)-*trans*-dendrochrysine **1.62**[54] from trienes **1.57** and **1.60** respectively. The second example is a particularly attractive application of this strategy as two pyrroline rings are constructed in a single step.

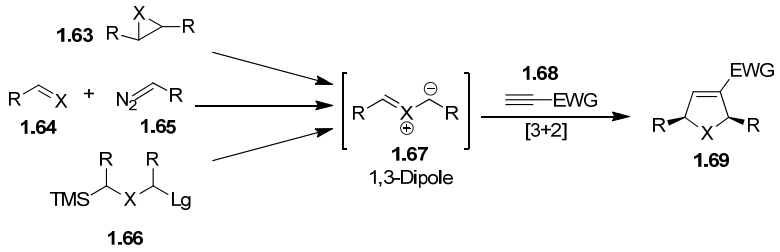


Scheme 1.7: Natural Product Total Synthesis Using Ring Closing Metathesis

1.3.2 [3+2] Dipolar Cycloadditions

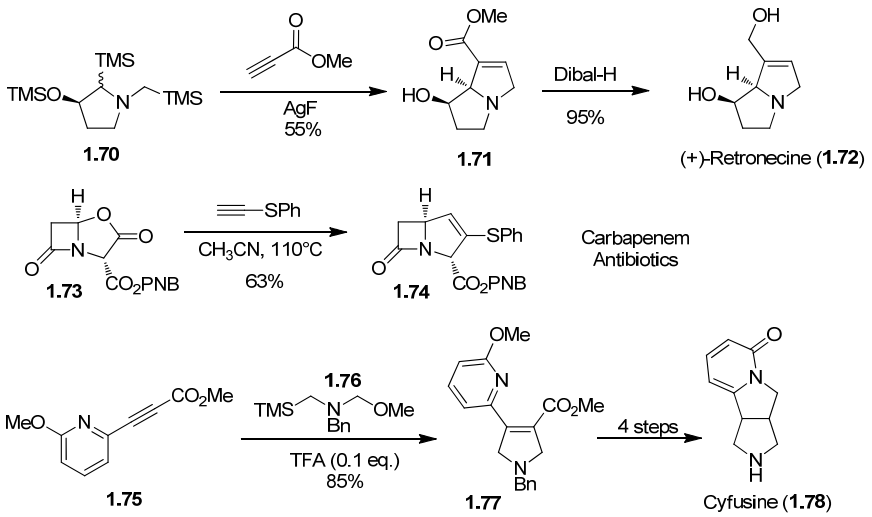
Dipolar cycloadditions are an important class of reactions within the field of organic chemistry.[55] Prominently featured as a member of this class are [3+2] dipolar cycloadditions. Dipoles such as **1.67** (Scheme 1.8, X = O, S, N), when coupled with an alkyne (**1.68**) provide ready access to 2,5-dihydro- furan, thiophene, and pyrrole products (**1.69**).[56] Although most reported examples are on generating and using azomethine ylides for constructing 2,5-dihydropyrroles. Generating the requisite 1,3-dipole (**1.67**) is one of the main challenges for this approach. Summarized in Scheme 1.8 are the three most commonly used strategies for generating the dipole. Thermal or Lewis acid catalyzed opening of oxiranes or aziridines (**1.63**) have been reported extensively.[57] This approach is not very general and requires very specific functionalization to proceed favorably. Imines, carbonyl, and thiocarbonyl groups (**1.64**) can be converted in a single step to **1.67** upon treatment with the appropriate metalcarbene, which in most cases originates from a diazo precursor (**1.65**).[58] This strategy is most commonly employed for carbonyl starting materials. The third approach, which relies on precursors such as **1.66** (Lg = leaving group) is the preferred method for accessing azomethine ylides. Another major challenge of this approach is

reactivity and regioselectivity. In most cases symmetrical activated alkynes such as acetylene dicarboxylates or diphenylacetylenes are needed. In general, this synthetic strategy is almost exclusively used to synthesize 2,5-dihydropyrroles, although intramolecular oxonium ylide variants have been popularized by Padwa and coworkers.[59] If the above conditions are met functional group compatibility tends to be good.



Scheme 1.8: Synthesis of 2,5-Dihydro- Furans, Thiophenes, and Pyrroles Using [3+2] Cycloadditions

This synthetic approach has found its place in natural product synthesis, but as is evident from the three examples in Scheme 1.9 these cases have been primarily limited to alkaloid synthesis. The natural product retronecine has been assembled in two steps from a trisilylated pyrrolidine (**1.70**). The intermediate azomethine ylide was generated using silver fluoride and then trapped with methyl propiolate to form pyrrolizidine core **1.71**.[60] In an interesting approach, the core of carbapenam antibiotics (**1.74**) was assembled from oxazolidone **1.73**. The dipole was generated by thermolysis of **1.73**, which released carbon dioxide and allowed trapping of the ylide with an alkyne.[61] As part of a vigorous research program, which recently resulted in the approval of varenicline (Chantix®), researchers at Pfizer have used an azomethine ylide approach to rapidly assembly a novel cytisine inspired structure (cyfusine **1.78**). Ynoate **1.75** and silyl aminal **1.76** were coupled under acidic conditions to form **1.77**, which was then converted in four additional steps to cyfusine.[62]

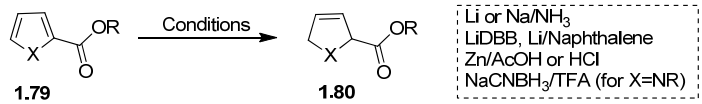


Scheme 1.9: Natural Product Total Synthesis Using [3+2] Cycloadditions

1.3.3 Birch Reductions

The dissolving metal reduction (Birch reduction) of furans, pyrroles, and thiophenes is one of the earlier reported strategies for accessing the target building blocks (Scheme 1.10).[63] Classically these dissolving metal reductions are performed in the presence of sodium or lithium in ammonia, although now lithium di-*tert*-butylbiphenyl (DBB) or similar reagents are more likely to be used. Many of these aromatic compounds can also be reduced without using dissolving metals. In such cases, the reagents of choice are commonly zinc or sodium cyanoborohydride. The nature of substituents tends to be critical for success. For all practical purposes this otherwise attractive approach tends to be mostly limited to substrates having at least one electron withdrawing group in the 2- position of the aromatic ring. What is particularly attractive about this approach is that the *in situ* generated carbanion can be trapped with useful electrophiles. This reductive strategy can be accomplished asymmetrically using either a chiral proton source or chiral auxiliary. When these promising asymmetric solutions are coupled with an *in situ* alkylation it seems clear

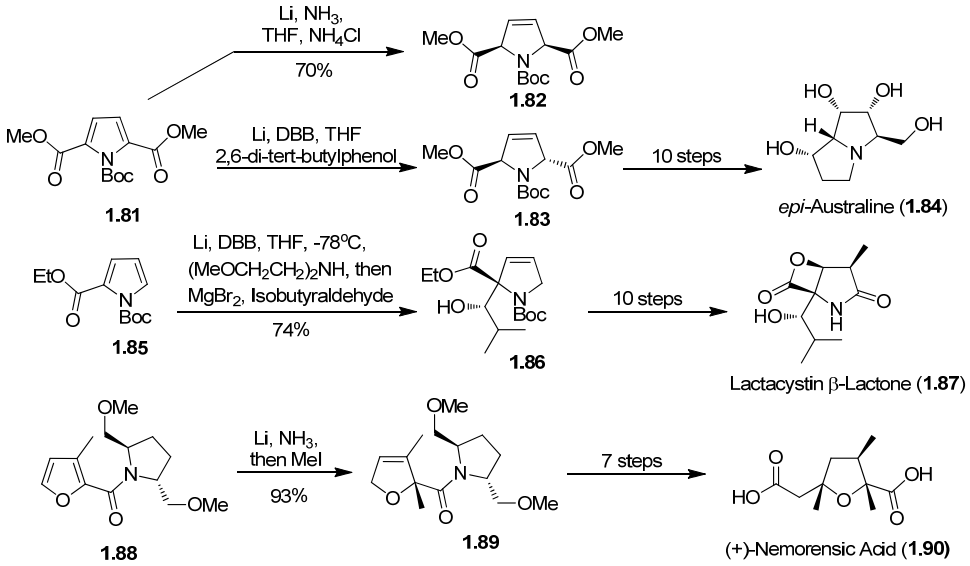
that this strategy can hold its own against other methods for a range of useful substrates.



1.79 1.80

Scheme 1.10: Birch Reduction of Aromatic Building Blocks

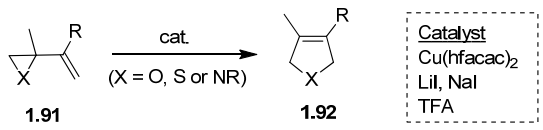
Donohoe and coworkers have led the way in this area for some time now, which is reflected by the fact that all the examples detailed in Scheme 1.11 are the work of his research group. Showcasing the strengths of this strategy, Donohoe has demonstrated that symmetrical pyrrole substrates (**1.81**) can be reduced to either the 2,5-*cis* (**1.82**) or 2,5-*trans* (**1.83**) products by using the appropriate reducing agent and proton source.[64] The *trans*-pyrroline (**1.83**) has been advanced to the natural product *epi*-australine.[65] In his synthetic approach towards the lactacystin β-lactone the intermediate anion generated during the reduction process is coupled *in situ* with isobutyraldehyde to afford **1.86** as a single diastereomer.[66] In his synthetic approach towards the natural product nemorensic acid Donohoe uses a C2-symmetrical pyrrolidine chiral auxiliary (**1.88**) to very effectively (30:1 dr) control the methylation of the anion generated during the Birch reduction.[67] Intermediate **1.89** was then advanced to the natural product in seven additional steps. Although these are all very impressive applications of this synthetic strategy they also very clearly highlight the fact that this approach is not yet very practical for aromatic precursors lacking an electron withdrawing group.



Scheme 1.11: Natural Product Total Synthesis Using Birch Reductions

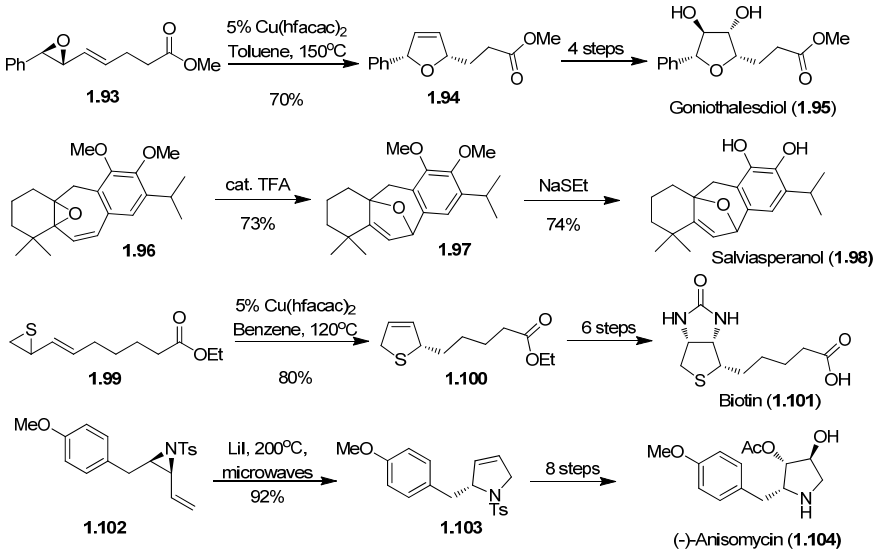
1.3.4 Vinyl- Oxirane, Thiirane, and Aziridine Rearrangements

Our research group has recently demonstrated that a wide range of vinyl-oxirane,[68] thiirane[69] and aziridine[70] substrates (Scheme 1.12, **1.91**) can be rearranged efficiently to the corresponding 2,5-dihydro- furan, thiophene, and pyrroline products (**1.92**) by using copper(II) hexafluoroacetylacetonate as a catalyst. Prior to our work in this area there were scattered reports of success for a narrow range of vinyl- oxirane and aziridine substrates, but there were no reports of a vinyl thiirane rearrangement. For example, it has been known since the 1960's that certain simple vinyl aziridines can be rearranged thermally[71] under very forcing conditions and in the 1980's Oshima showed that triene monoaziridines can be rearranged in the presence of a palladium catalyst,[72] while simple vinyl aziridines did not. Acid catalyzed vinyl oxirane rearrangements have been known for a long time. Most of these examples are rigged for success in that the detrimental competing hydride shift cannot occur. Our copper catalyzed rearrangement is the optimal approach for all substrate categories and again the only approach that can be applied to vinyl thiiranes.



Scheme 1.12: Rearrangement of Vinyl- Oxiranes, Thiiranes, and Aziridines

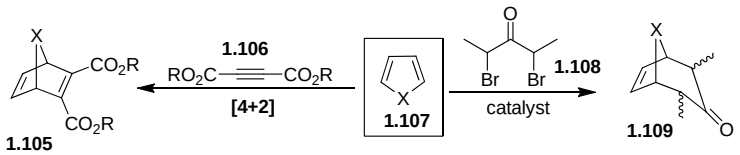
This powerful synthetic strategy has also found its place in the field of natural product total synthesis (Scheme 1.13). Our group has recently completed the total synthesis of goniothalesdiol by stereoselectively rearranging vinyl oxirane **1.93** to 2,5-dihydrofuran **1.94**, which could be converted to the natural product in four additional steps.[73] Sarpong and coworkers used trifluoroacetic acid to ring expand **1.96** to oxabicyclic product **1.97** in their synthetic approach towards salviasperanol.[74] Yields are high for this substrate since the competing hydride shift is not possible. Majetich used the same conditions for a similar substrate in his approach towards salviasperanol.[75] We showcased our novel copper catalyzed vinyl thiirane rearrangement by converting **1.99** to 2,5-dihydrothiophene **1.100** *en route* to a formal synthesis of biotin.[36] Somfai has shown that vinyl aziridine **1.102** can be rearranged under microwave conditions to pyrroline **1.103** in the presence of lithium iodide.[76] He then advanced this product to an intermediate in Hall's total synthesis of anisomycin.[77]



Scheme 1.13: Natural Product Total Synthesis Using Vinyl- Oxiranes, Thiiranes, and Aziridines

1.3.5 [4+2] and [4+3] Cycloadditions

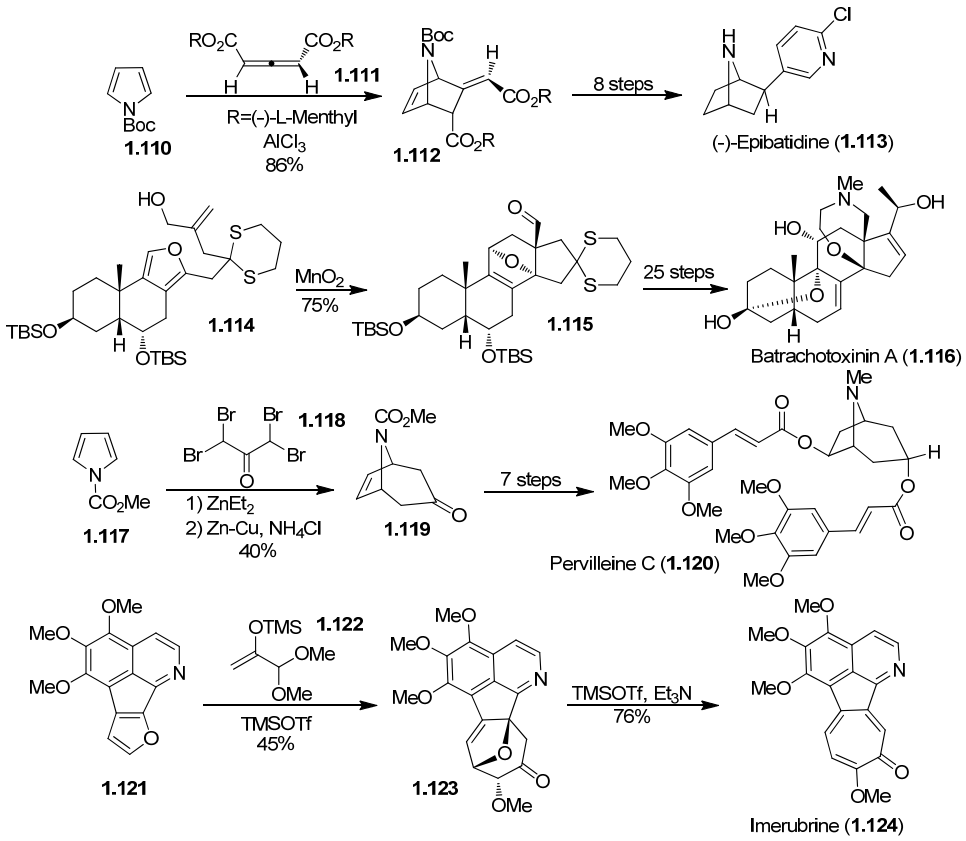
Although [4+2] and [4+3] cycloadditions of furans, thiophenes and pyrroles provide access to a very narrow spectrum of 2,5-dihydro- furan, thiophene, and pyrrole products, we have included these two cycloaddition approaches in our survey because the resulting oxa-, aza, and thiabicyclic products are hard to access using other methods (Scheme 1.14). These two approaches do not work very well for thiophenes,[78] although this limitation can be partly remedied by using sulfone derivatives.[79] The Diels-Alder reaction of furans and pyrroles require in most cases very active dienophiles for the reaction to succeed.[80] The oxyallyl cations classically used for [4+3] cycloadditions can be generated in many different ways, but originate in most cases from halo ketones or similary activated ketone precursors.[81] These halo ketones are converted to the oxyallyl cation by treatment with zinc metal. This approach is in most cases limited to simple substitution patterns and many functional groups are not well tolerated.



Scheme 1.14: [4+2] and [4+3] Cycloadditions of Furans, Thiophenes, and Pyrroles

These cycloadditions have been used for the total synthesis of a number of natural products (Scheme 1.15). Epibatidine has served as a favored playground for evaluating different synthetic methods and strategies. Azabicyclic product **1.112** was nicely assembled by fusing chiral allene **1.111** to pyrrole **1.110** in the presence of aluminum trichloride.[82] This intermediate was then advanced to a known ketone that had previously been converted to epibatidine by Trudell and coworkers.[83] Kishi employed furan **1.114** as a dienophile in an intramolecular Diels-Alder reaction with an *in situ* generated methacrolein moiety. The resulting product (**1.115**) was then

eventually converted to batrachotoxinin A.[84] The anti-cancer agent pervilleine C was recently synthesized. Its tropane core (**1.119**) was constructed by coupling pyrrole **1.117** with tetrabromoketone **1.118** and the resulting cycloadduct was debrominated.[85] By reacting the oxyallyl cation generated from **1.122** with furan **1.121** the natural product imerubrine was efficiently assembled. The oxabicyclic cycloadduct (**1.123**) was then converted in a single step to the natural product.[86]

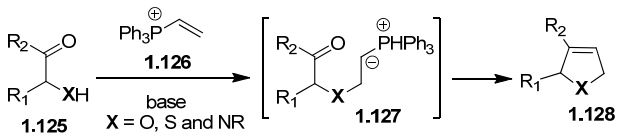


Scheme 1.15: Natural Product Total Synthesis Using [4+2] and [4+3] Cycloadditions

1.3.6 Vinyl Phosphonium Cascade

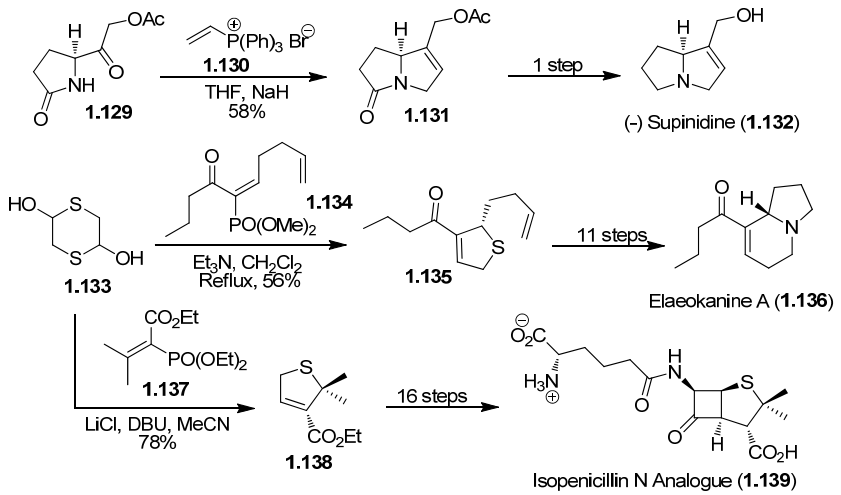
In the 1960's Schweizer demonstrated that various nucleophiles, including R_2NH, RSH, ROH, and R_2PH could be added to vinyl phosphonium salts (**1.126**, Scheme 1.16). When a carbonyl (**1.125**) was tethered to these nucleophiles the ylide generated *in situ* underwent a Wittig olefination, thus allowing ready access to all three heterocycle families (**1.128**) in a single operation.[87] This is an attractive two

component coupling reaction using readily available starting materials. When amines and alcohols are used as nucleophiles the vinylphosphonium salt is often activated by an additional stabilizing group such as arylsulfones and arylsulfoxides to ensure a successful Michael addition step. This coupling strategy suffers when the vinyl phophonium salt is substituted in the β-postion, although thiols are in most cases sufficiently nucleophilic to be successful. The phosphonium salt in certain situations can be replaced by the phosphoryl ester with comparable results. Amine nucleophiles, in order to be competent, must be electron deficient such as amides or sulfonamides. This method is one of the better methods discussed to construct 2,5-dihydrothiophenes.



Scheme 1.16: Vinyl Phosphonium Cascade

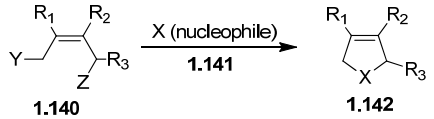
This exciting synthetic approach has also found its place in natural product synthesis (Scheme 1.17). Hewson nicely demonstrated that the pyrrolizidine alkaloid supinidine can be rapidly assembled in two steps from lactam **1.129**.[88] Dihydrothiophenes **1.135** and **1.138** were both accessed in a single step from 1,4-dithiane-2,5-diol (**1.133**) upon treatment with vinyl phosphonates **1.134** and **1.137** respectively. Enone **1.135** was advanced to elaeokanine A[89] while enoate **1.138** was further functionalized to isopenicillin analogue **1.139**.[90]



Scheme 1.17: Natural Product Total Synthesis Using a Vinyl Phosphonium Cascades

1.3.7 Nucleophilic Displacements

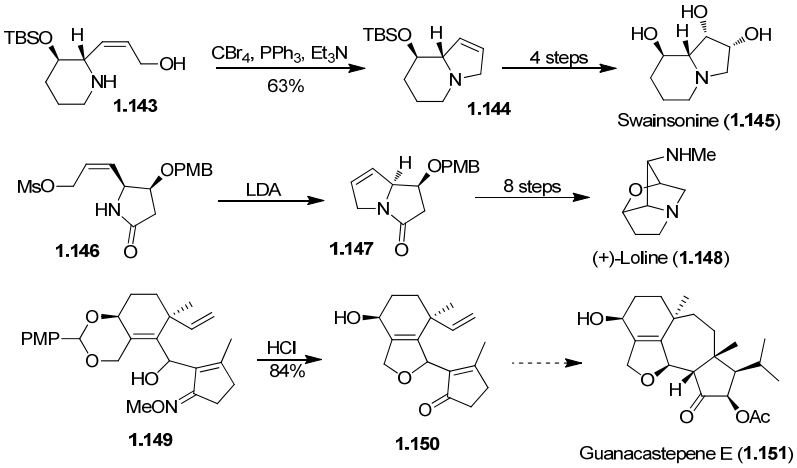
One of the oldest approaches to 2,5-dihydrofurans, thiophenes, and pyrroles is a simple nucleophilic displacement using either an internal or external nucleophile (Scheme 1.18). By using an appropriately functionalized *Z*-olefin with two leaving groups (Y and Z, **1.140**) a sulfur or nitrogen based nucleophile (X, **1.141**) can be used to form the product (**1.142**) directly. In practice, this method is rarely used and those few literature examples are mostly limited to the unsubstituted case. More commonly Y or Z is the desired heteroatom and the other is the leaving group such as a halide, sulfonate ester, or a hydroxy group. What makes this synthetic approach most unattractive is the need for a multistep route for constructing a highly functionalized *Z*-olefin (**1.140**). Once precursors like **1.140** are accessed the cyclization tends to occur without problems.



Scheme 1.18: Nucleophilic Displacements

Three natural product examples utilizing this strategy are presented in Scheme 1.19. Swainsonine's fused bicyclic core was completed by *in situ* activation and

cyclization of allylic alcohol **1.143** to **1.144**.[91] Substrate controlled dihydroxylation and protecting group manipulations then afforded the natural product. A similar core (**1.147**) was stitched together by cyclizing a lithiolactam onto an allylic sulfonate ester (**1.146**). White and coworkers then advanced this intermediate to the bridged bicyclic alkaloid (+)-loline.[92] In his approach towards the guanacastepene family of natural products, Sorensen cyclized a triene triol (**1.149**) to a fused 2,5-dihydrofuran (**1.150**).[93]

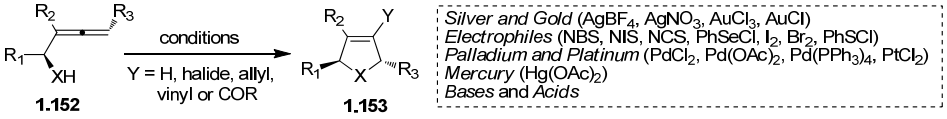


Scheme 1.19: Natural Product Total Synthesis Using Nucleophilic Displacements

1.3.8 Allene Cyclizations

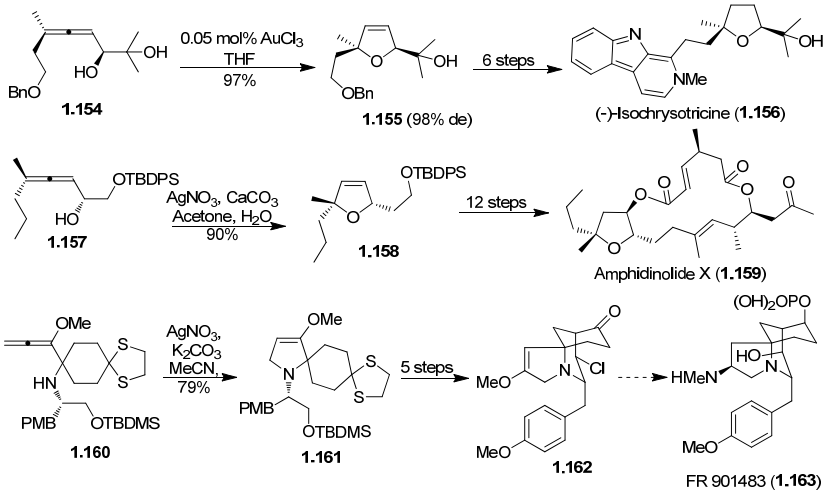
The cyclization of an allenic alcohol (**1.152**, Scheme 1.20) to a 2,5-dihydrofuran (**1.153**) in the presence of either a base[94] or mercury salts[95] was first reported forty years ago. In 1979 Claesson demonstrated that pyrrolines could be accessed similarly upon treatment with Ag(I) catalysts.[96] In the late 1980's Liebeskind and coworkers reported that palladium catalyzed this cyclization and that the resulting vinyl palladate could be cross-coupled *in situ* with an olefin (Y = vinyl).[97] Since then a number of halide, selenium, and sulfur electrophiles have also been shown to aid this cyclization while at the same time incorporating a functional handle (Y = Cl, Br, I, PhS, PhSe).[98] This powerful transformation has been revisited in the last eight years as part of what could only be described as a gold[99] and silver[100] catalyst rush. For

example, Krause has shown Au(I) and Au(III) catalysts to be ideally suited for 2,5-dihydrothiophene formation.[101] These efforts have greatly expanded the scope of this transformation, which in our minds firmly ranks as one of the best current methods to access 2,5-dihydro- furans, thiophenes, and pyrroles.



Scheme 1.20: Cyclizations of Allenic Alcohols, Amines, and Thiols

The allene precious metal rush has not surprisingly found its way to natural product total synthesis. Shown in Scheme 1.21 are three nice applications of this useful cyclization approach. Krause has used a gold(III) catalyst to cyclize allene **1.154** in high yield and stereoselectivity to dihydrofuran **1.155** *en route* to the natural product (-)-isochrysotricine.[102] Fürstner and colleagues have used the classic silver nitrate cyclization conditions to advance allenic alcohol **1.157** to dihydrofuran **1.158**. This key intermediate was then utilized to complete the first total synthesis of amphidinolide X.[103] Although **1.162** has not been converted to FR 901493, Reissig has showcased an efficient cyclization of amino allene **1.160** to pyrrolidine **1.161** that could then be converted in five additional steps to **1.162**.[104]

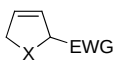


Scheme 1.21: Total Synthesis of Natural Products Using Allene Cyclizations

1.3.9 Conclusions

For a chemist planning to use any of these methods in a synthesis, perhaps one of the best ways to summarize the strengths and weaknesses of the eight synthetic approaches discussed in this section is to graphically tabulate this information. We have chosen the five product classes shown in Table 1.5 as indicators of the effectiveness of these methods. Our ranking system uses (++), (+), and (–) as grades of a very good, fair, and no match of the reaction of interest for a given substrate class. This graphic presentation also serves very well to highlight the need for further improving existing methods and to develop new approaches. For many of these substrate classes there are no good choices. For example, when one considers the bridged bicyclic substrate class there are not many choices. We are particularly proud of the fact that our contributions to this area, the copper catalyzed rearrangement of vinyl- oxiranes, thiiranes and aziridines allows access to all five product classes. It is important to note that this table does not factor in the difficulty of preparing the synthetic precursors or factors such as cost, toxicity, scaleability, or solvent use. Inclusion of these factors would be quite complex and would undoubtedly further highlight just how much need there is for better methods.

Table 1.5: Comparison of the Eight Synthetic Approaches

Synthetic Approaches					
Ring Closing Metathesis (RCM)	++	++	-	-	+
[3+2] Cycloaddition	-	+	-	+	++
Birch Reduction	-	+	-	-	++
[1,3]-Rearrangement	++	+	+	++	+
[4+2]/[4+3] Cycloadditions	-	-	++	-	-
Vinylphosphine Cyclization Cascade	+	-	-	+	+
Nucleophilic Substitution	+	-	-	+	+
Allene Cyclization	+	+	-	+	+

(++) = very good, (+) = fair, (–) = no match

1.4 Copper (II) bishexafluoroacetylacetone

Copper has been a popular metal for a number of metal catalyzed reactions in both the +1 and +2 oxidation states.[105] For example the copper catalyzed conjugate addition of Grignard reagents, Huisgen alkyne-azide cycloaddition, decomposition of diazo-alkanes, Sonogashira cross-coupling, and the activation of aryl halides are some of the most popular.[106] Copper (II) bis-hexalfuoroacetylacetonate is a commercially available compound that contains an electrophilic metal center. The crystal structure of anhydrous $Cu(hfacac)_2$ (Figure 1.4) reveals that it is a square planar complex with a great affinity for donor ligands as exemplified by close intermolecular interaction with fluorine on another ligand.[107] However, it is usually sold as a hydrate (5g for $41 from Aldrich), with the *mono*-hydrate existing as a square pyramidal complex with an apical water molecule.

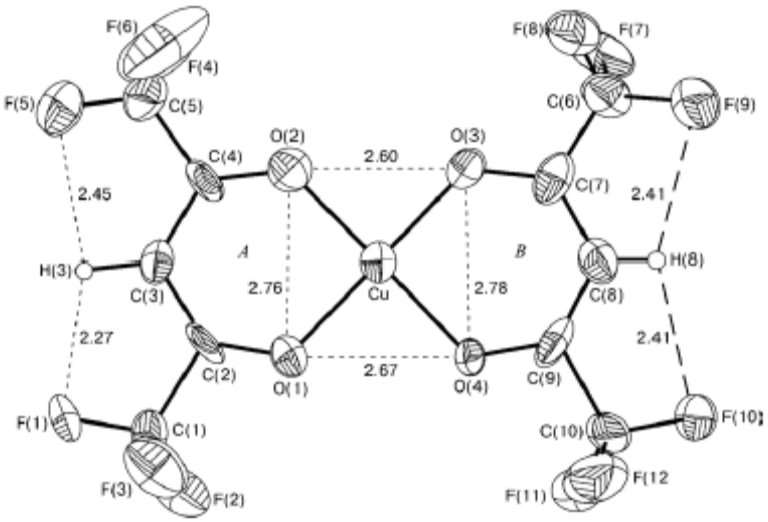
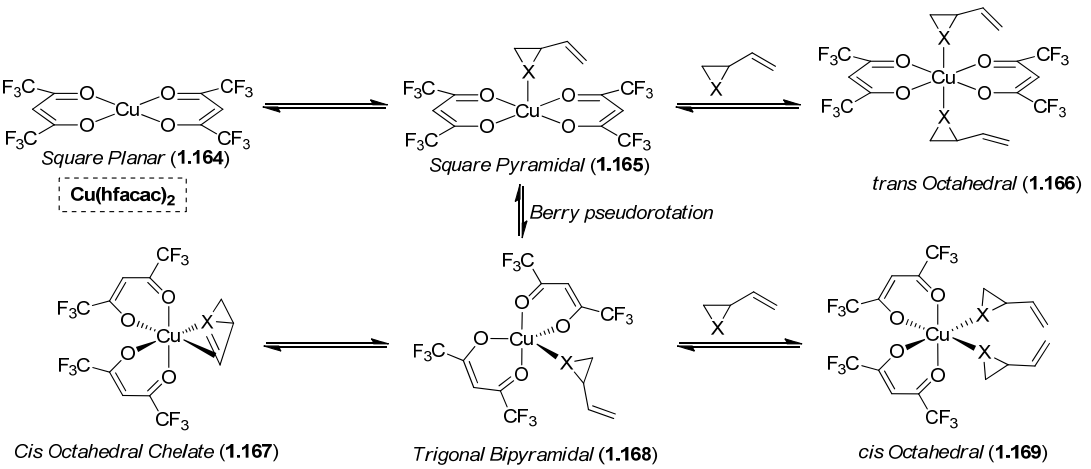


Figure 1.4: Crystal Structure of anhydrous $Cu(hfacac)_2$

It has been known for a long time that $Cu(hfacac)_2$ binds a second nitrogenous ligand with great ease, where most other copper (II) centers will not.[108] Upon treatment with excess of such ligands usually *trans*- or *cis*-octahedral $Cu(hfacac)_2L_2$ complexes are formed. The ligand-complex outcome is dependent on the nature of the

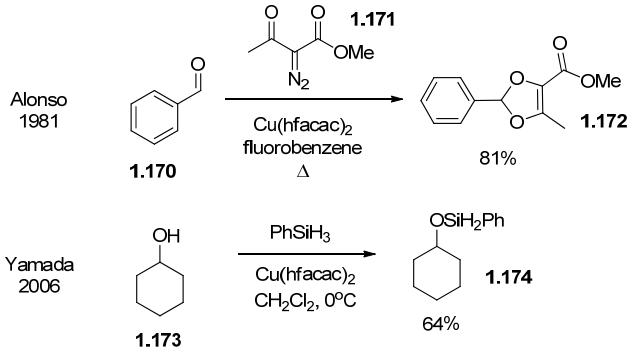
added ligand. Pyridine and chelating diamines prefer to form *cis*-octahedral complexes,[109] while pyrazine prefers to form an oligomeric network of *trans*-octrahedral units.[110] Interestingly, when ammonia or *t*-butyl amine are mixed with $Cu(hfacac)_2$ a trigonal bipyramidal complex is formed with the amine ligand at the basal position.[111] When 2-ethynyl pyridine is used it acts as a bidentate ligand with a slightly distorted trigonal bipyramidal complex with the nitrogen occupying the apical site thus bringing the alkyne substitutent in close proximity to the metal center.[112] Although there are no crystal structures of copper(II) olefin complexes they can be observed using a number of spectroscopic techniques.[113] With the knowledge presented in this paragraph we can expect that addition of a vinyloxirane, vinylazridine, or vinylthiirane to exist in a complex equilibrium. Scheme 1.22 shows the possible geometries that the Cu (II) catalyst may adopt in the presence of these.



Scheme 1.22: Structurally Relevant Substrate-Catalyst Complex Scenarios for $Cu(hfacac)_2$

Despite the intensive study of the structure and reactivity of $Cu(hfacac)_2$ it has not been used as a catalyst extensively. Shown in Scheme 1.23 are the two modes of catalysis known for $Cu(hfacac)_2$ prior to investigation by the Njardarson group. Alonso first discovered that $Cu(hfacac)_2$ was effective at decomposing stabilized diazo

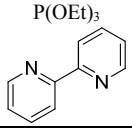
compounds to the metal associated carbenoid intermediate.[114] These carbenoids have subsequently been shown to undergo cyclopropanations, insertions into X-H bonds (X = C, N, O, S), and 1,3-dipolar cycloadditions. A second catalytic mode of reactivity was discovered by Yamada where a dehydrogenative coupling of alcohols and phenylsilane was observed.[115] The primary use of $Cu(hfacac)_2$ has been for chemical vapor deposition of metallic copper.[116]



Scheme 1.23: Known Reactions Catalyzed by $Cu(hfacac)_2$

As mentioned above $Cu(hfacac)_2$ readily binds additional ligands and several methods have been used to measure the binding constants and enthalpy associated with these interactions. Table 1.6 displays the results of several Lewis bases binding to $Cu(hfacac)_2$ which may be relevant to the subsequent chapters of this thesis. We observe that increased fluorination of the ligands on copper increases the equilibrium constant with only a modest enthalpy effect. We observe that $Cu(hfacac)_2$ is unique in its ability to bind a second base (entry d) and the ability to bind very week donor groups like olefins (entry e). Hard nucleophiles (entry g) are preferred to soft nucleophiles (entry f). Lastly, bidentate ligands (entry k) are readily bound by $Cu(hfacac)_2$

Table 1.6: Binding of Lewis Bases to Copper (II) Acetylacetonate Complexes

Entry	Copper Complex	Base	Solvent	K (L/mol)	-ΔH (kcal/mol)
a[117]	$Cu(acac)_2$		Benzene	4.7	6.5
b[117]	$Cu(tfacac)_2$		Benzene	701	7.4
c[117]	$Cu(hfacac)_2$		Benzene	$>10^5$	9.1
d[117]	$Cu(hfacac)_2 \cdot py$		Benzene	780	9.4
e[118]	$Cu(hfacac)_2$		Chloroform	1.2	ND
f[119]	$Cu(hfacac)_2$		*o*-Dichlorobenzene	99	4.6
g[119]	$Cu(hfacac)_2$		*o*-Dichlorobenzene	3500	7.2
h[119]	$Cu(hfacac)_2$		CCl_4	$>10^7$	15.5
i[119]	$Cu(hfacac)_2$	EtOAc	CCl_4	190	5.9
j[119]	$Cu(hfacac)_2$	$P(OEt)_3$	*o*-Dichlorobenzene	420	5.5
k[117]	$Cu(hfacac)_2$		Benzene	ND	19.1

ND = Not Determined, $Cu(acac)_2$ = Copper (II) bisacetylacetonate, $Cu(tfacac)_2$ = Copper (II) bistrifluoroacetylacetonate, $Cu(hfacac)_2$ = Copper (II) bishexafluoroacetylacetonate, Py = Pyridine

Based on these structural and reactivity characteristics, $Cu(hfacac)_2$ seems ideally suited for the ring expansion of vinyloxiranes, aziridines, and thiiranes. By investigating and developing this method, heterocycles containing oxygen, nitrogen, and sulfur will be readily synthesized.

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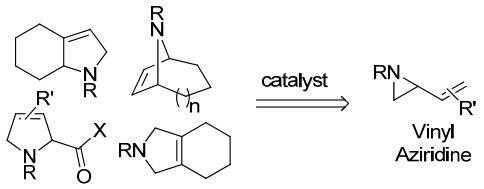
Chapter 2

Lewis Acid Catalyzed [1,3]-Sigmatropic Rearrangement of Vinylaziridines

2.1 Background and Significance

3-Pyrrolines (2,5-dihydropyrroles), while important in their own right, are versatile intermediates for the synthesis of pyrrolidines and pyrroles.[1] Collectively these ring systems occur in countless natural products and pharmaceuticals.[2] Not surprisingly, several different synthetic approaches toward pyrrolines have been developed, the most popular of which are Birch reduction of pyrroles,[3] [3+2] cyclization,[4] and ring closing metathesis.[5] Despite these and other creative approaches, a need exists for a simple and selective method which allows access to structurally complex 3-pyrrolines. Herein, we demonstrate that vinyl aziridines can be efficiently converted to 3-pyrrolines using commercially available copper(II) catalysts.



Scheme 2.1: General Scheme for 3-Pyrroline Synthesis

Analogous to the vinylcyclopropane rearrangement,[6] the thermolysis of vinyl aziridines to 3-pyrrolines was first observed in the late 1960's.[7] Harsh thermal conditions were employed and little substrate scope was observed. Since these initial experiments, several attempts have been made to investigate the reaction further, but limitations such as competing side reactions and the necessity of additional functionality were found.[8] Therefore, applications of this rearrangement to the synthesis of complex molecules have been lacking.[9,10] Clearly, there is a need to develop conditions that expand the scope of the rearrangement and allow functional group compatibility.

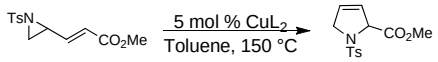
Vinyl aziridines are most easily synthesized by one of three methods: the addition of a nitrene to a diene, the addition of an allylic ylide to an imine, or the

cyclization of unsaturated amino alcohols.[11] Each method has limitations often directly related to the nitrogen protecting group. Our efforts focus on the p-toluenesulfonyl (Ts) and phthalimido (PhthN) protecting groups. Tosyl aziridines are easily accessed by employing an aziridination protocol developed by Sharpless[12] or by catalytic decomposition of N-phenyliodinanes.[13] Although phthalimide substituted aziridines are less commonly used, they offer an attractive option based on their ease of synthesis utilizing a stabilized singlet nitrene and broader substrate scope.[14]

2.2 Results and Discussion

Vinyl aziridine **2.1** was chosen as a model substrate due to the growing interest in dehydroprolines.[15] Based on previous work by our group on the catalytic ring expansion of vinyl oxiranes and vinyl thiiranes,[16] copper catalysts were tested (Table 2.1). The more electrophilic copper(II) hexafluoroacetylacetonate (entries 14-18) proved far superior to other commercially available and synthetic catalysts. Interestingly, the reaction proceeds faster and with a higher yield when the $Cu(hfacac)_2$ hydrate is dried prior to use. Optimized reaction conditions were found to be 150 °C, 0.1 M [substrate], and 5 mol % catalyst loading.

Table 2.1: Copper Catalyzed Ring Expansion of Vinylaziridines



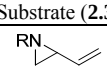
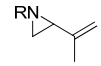
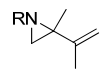
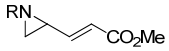
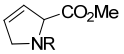
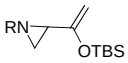
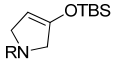
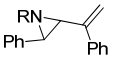
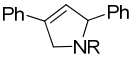
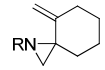
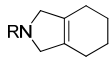
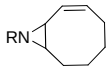
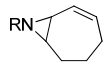
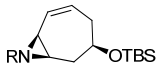
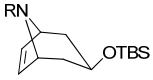
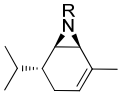
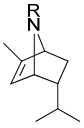
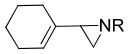
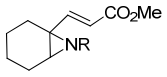
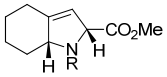
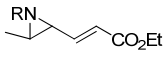
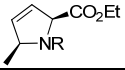
2.1 **2.2**

entry	catalyst	time (h)	yield[a]
1	none	16	0%[b]
2	CuI	16	0%
3	Cu[(S,S)-Ph-box]Cl_2	16	0%
4	Cu[(S,S)-Ph-box]OTf_2	16	0%
5	Cu$(acac)_2$	16	0%
6	Cu$(tfacac)_2$	16	0%
7	Cu$(dbm)_2$	16	10%
8	Cu$(ptfm)_2$	16	0%
9	Cu$(accy)_2$	16	35%
10	Cu$(tfaccy)_2$	16	20%.
11	Cu$(fod)_2$	16	0%
12	Cu(3-[NO_2]acac)$_2$	16	0%
13	Cu(3-[CO_2Et]acac)$_2$	16	20%
14	Cu$(hfacac)_2 \cdot H_2O$	11	70%
15	**Cu$(hfacac)_2$ (dry)**	**7.5**	**99%**
16	Cu$(hfacac)_2$ (dry)	1[c]	99%
17	Cu$(hfacac)_2$ (dry)	22[d]	99%
18	Cu$(hfacac)_2$ (dry)	36[e]	99%

Conditions: 5 mol % catalyst, toluene, 150 °C, 0.1 M. [a] NMR Yield. [b] Decomposes at 170 °C. [c] 5 M. [d] 1 mol %. [e] 130 °C. { hf = hexafluoro, acac = acetylacetonate, (S,S)-Ph-box = (S,S)-2,2'-Isopropylidene-bis(4-phenyl-2-oxazoline), tf = trifluoro, dbm = dibenzoylmethanate, ptfm = 1,3-bis[4-(trifluoromethyl)phenyl]-1,3-propanedionate, accy = 2-acetylcyclohexanone, fod = heptafluorobutanoyl)pivaloylmethanate, 3-[NO_2]acac = 3-nitroacetylacetonate, 3-[CO_2Et]acac = ethyl diacetoacetate}

Table 2.2 displays the results of applying these optimized conditions to a variety of phthalimide and tosyl protected vinyl aziridines. These products can be readily deprotected to give the N-H pyrrolines.[17] Simple substrates (entries a-k) demonstrate that all substitution patterns are well tolerated resulting in excellent yields. Entries d, e, and h display an important synthetic aspect of this rearrangement, as each 3-pyrroline can originate from two regioisomeric vinyl aziridine precursors or even from their mixture. Some of the simple substrates can rearrange thermally at more extreme temperatures, but often at dramatically diminished yield. However, the thermal rearrangement of more complex substrates is often nonexistent.

Table 2.2: 3-Pyrroline Synthesis

Entry	Substrate (**2.3**)	Product (**2.4**)	R	T (°C)	Time (h)	yield
a			Ts	100	5.5	92%
b			PhthN	100	2	92%
c			Ts	100	1	99%
d			PhthN	100	2	92%
e			PhthN	100	3	96%
f			Ts	100	1	98%
g			PhthN	100	0.3	93%
h			PhthN	100	3	96%
i			Ts	150	12	80%
j[i]			Ts	150	7.5	98%
k[g]			PhthN	150	0.8	67%[k]
l			Ts	100	5	97%
m[g]			Ts	120	20	60%
n			Ts	120	6	95%[f]
o			Ts	150	20	75%[c]
p			PhthN	150	16	93%[d,e]
q			PhthN	150	12	94%[d]
r[a]			PhthN	150	21	53%
s[h]			PhthN	150	3	28%[f]
t[h]			PhthN	150	2	56%
u			Ts	150	1	78%
v			Ts	150	1.5	94%
w[a]			Ts	150	1	88% (>20:1 d.r.)
x[a,g]			Ts	150	16	90% (4:1 d.r.)

Conditions: 5 mol % dry $Cu(hfacac)_2$, 0.1 M in Benzene (100°C) or Toluene (120°C and 150°C). [a] Racemic. [b] Isolated yields. [c] $Cu(hfacac)_2 \cdot H_2O$ does not work. [d] 0.2 M. [e] 20 mol % $Cu(hfacac)_2$. [f] Thermal component to reaction. [g] Byproducts derived from the formation of azomethine ylides are observed in these reactions. [h] Pyrroles are formed from the retro Diels-Alder reaction in these reactions. [i] Unfortunately when compound **2.1** was synthesized asymmetrically, chirality was not transferred to the product as assessed by transesterification with a chiral alcohol. The product **2.2** was found not to epimerize under the given reaction conditions.

The copper catalyzed rearrangement has been shown to be quite functional group tolerant. These groups include enol ethers, esters, protected alcohols, sulfonamides, and imides. This compatibility is important because some of these functional groups likely coordinate to the electrophilic copper center and yet do not prevent the reaction from occurring. Next, fused and bridged bicyclic compounds (entries n-w) can be rearranged to create complex ring systems. With respect to protecting groups, we observe that in general the more electron-rich phthalimide aziridines rearrange faster than the corresponding tosyl protected aziridines. Product yields vary between protecting groups, but only phthalimide aziridines are competent for very strained systems (entries q-t). Entries w and x are particularly noteworthy, since they establish the potential for diastereoselective rearrangements. Lastly, the diastereomer of the substrate in entry r and the *Z*-isomer of the substrate in entry j do not rearrange under a variety of conditions tested. These substrates display the importance of the conformation and sterics of the vinylaziridine when it is bound to the catalyst.

Investigation into this reaction has revealed that the rearrangement is copper specific and with a few exceptions distinct to copper(II) acetylacetone ligands. Determination of the mechanism has proved elusive, but the synthesis of two new catalysts has probed what the active copper species might be. Substrate **2.3c** was chosen as a model system for investigation and the results are shown in Figure 2.1. The reaction was conducted in sealed NMR tubes under the standard reaction conditions except $CDCl_3$ was used as the solvent. Plotting the reaction progress with $Cu(hfacac)_2$ (**2.5**) reveals a characteristic sigmoidal shape suggesting an autocatalytic process. When the catalyst loading is changed a dramatic effect on the rate is observed. When a mixed acac catalyst is used, Cu(dbm)(hfacac) (**2.6**)[18], a slightly slower reaction is observed with a similar profile. Careful analysis of the slope of the

line suggests the maximum rate of the reaction is higher than that of $Cu(hfacac)_2$. This suggests that a more active catalyst species is produced during the course of the reaction. The reaction profile of Cu(hfacac)(TMEDA)Br (**2.7**)[19] is completely different with little to no induction period or autocatalytic behavior. This suggests that the catalyst is already in its most active form unlike $Cu(hfacac)_2$. This catalyst is inferior likely due to a less electrophilic copper(II) center. The mixed complexes, **2.6** and **2.7**, are peculiar since no other catalysts have even approached the effectiveness of $Cu(hfacac)_2$ as demonstrated in Table 2.1. Finally, similar kinetic experiments were performed in benzene and those experiments confirmed the same behavior; however improved solubility in $CDCl_3$ created more reproducible results.

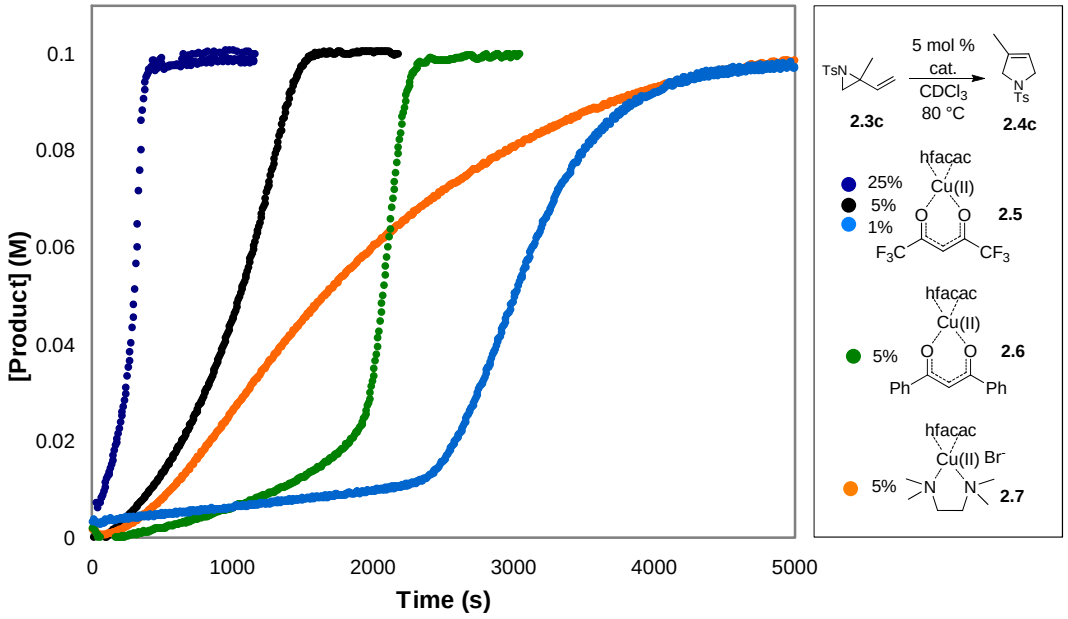
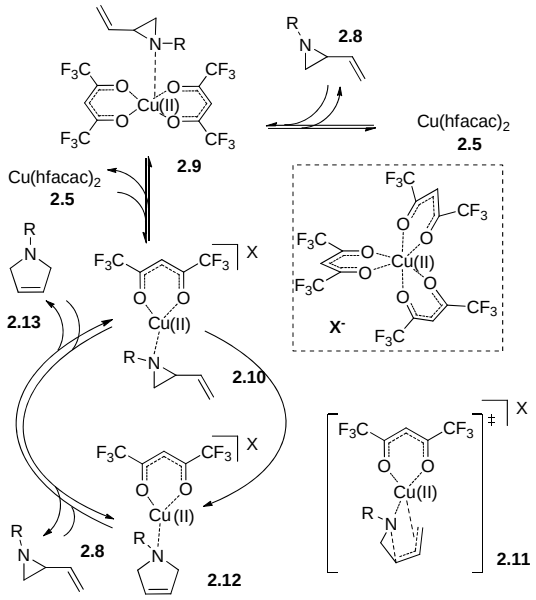


Figure 2.1**:** Kinetics plot of 2-Methyl-N-Tosyl-2-Vinylaziridine

Using all results obtained during this investigation we have produced a catalytic cycle shown in Scheme 2.2. We propose that substrate (**2.8**) binds in the axial site of $Cu(hfacac)_2$ to form complex **2.9**. The substrate induces disproportionation of the $Cu(hfacac)_2$ to form cationic copper(II) complex **2.10** and anionic copper(II)

complex $\mathbf{X}^-$, which serves as a counterion for the active cationic complex. This *in situ* generated cationic copper(II) catalyst through a Lewis acid activation weakens the C-N bond of the aziridine. During the ring expansion, it is possible that the copper center may chelate to the nearby olefin producing the transition state **2.11**. We believe that an ordered transition state, without complete heterolysis or homolysis of the C-N bond, is necessary to account for the diastereoselectivity observed in the rearrangement of substrates **2.3w** and **2.3x**. The rearrangement produces complex **2.12**, which then undergoes an associative interchange with more substrate to reform complex **2.10**. Complexes **2.10** and **2.12** constitute the autocatalytic cycle that we propose is in good agreement with the observed kinetics presented in Figure 2.1. Complexes **2.10** and **2.12** cannot be observed during the course of the reaction because of the paramagnetic behavior of copper(II).



Scheme 2.2**:** Proposed Catalytic Cycle

This proposed mechanism accounts for a number of other experimental observations not yet mentioned. First, product **2.13** was found to inhibit the reaction dramatically. Second, X^- was found to not be catalytically competent when

synthesized independently.[20] Also, reactions with cationic copper(II) complex **2.7** do not possess an induction period because it mimics the structure of **2.10** which is the active catalyst. Next, copper(II) species are observable (UV-Vis. Spectroscopy, NMR) throughout the reaction, but no copper(I) intermediates could be detected nor were copper(I) catalysts competent in the rearrangement. Finally, using Singleton's method[21] we have obtained preliminary kinetic isotope results for two different vinyl aziridine substrates. These studies show significant heavy atom isotope effects at all three carbon centers involved in the rearrangement suggesting the reaction is concerted in nature.

In summary, we have demonstrated that 3-pyrrolines can be readily prepared from vinyl aziridines using commercially available copper(II) catalysts. The scope of this new catalytic rearrangement is very broad, providing access to a greater range of diverse products than other currently available 3-pyrroline forming methods. Mechanistic analysis revealed unique autocatalytic behavior and can be summarized as a Lewis Acid catalyzed [1,3]-sigmatropic rearrangement. New catalysts were synthesized based on these mechanistic insights. These catalysts approach the effectiveness of $Cu(hfacac)_2$, but allow more options for electronic tuning and induction of asymmetry. Further studies on the mechanism and scope of this ring expansion are currently underway.

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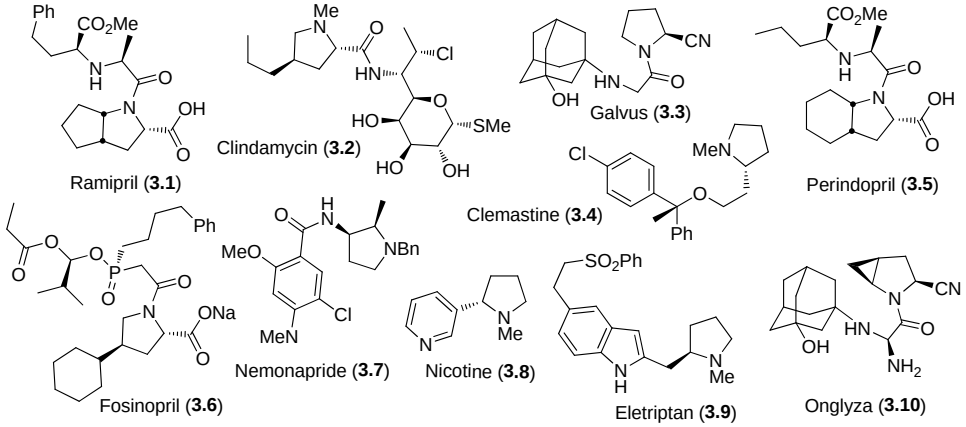
Chapter 3

Novel Asymmetric Synthesis of Common Pyrrolidine Pharmacophores

3.1 Background and Significance

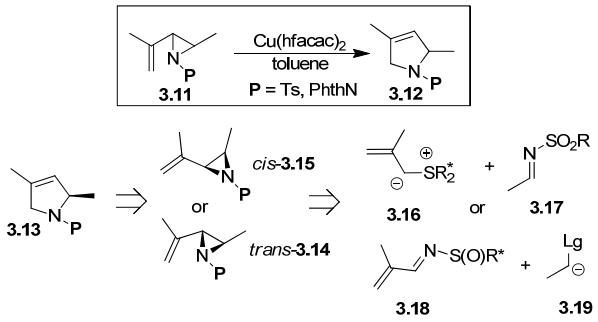
The pharmaceutical industry is undoubtedly the most important beneficiary of new synthetic methods. With a cursory review of the structural motifs of the top 200 selling drugs[1] it becomes quickly apparent that around 90% contain at least one nitrogen atom and approximately 65% are decorated with a heterocycle. Not surprisingly, the majority of these heterocycles are nitrogenous. In recent years the demand for practical asymmetric methods has increased dramatically[2] following regulatory agencies' call for enantiomerically pure drug candidates. Given the above cited structural preferences it is evident that the need for useful new methods that provide access to chiral nitrogen containing heterocycles is significant.

Chiral pyrrolidines are one of the most commonly used nitrogen containing heterocyclic pharmacophores (Scheme 3.1). The proline like features of a significant number of these motifs suggests that nature continues to serve well as a starting design template for privileged structural classes. Given the great success of chiral pyrrolidines as important pharmaceutical building blocks it follows that a range of practical methods[3] are needed in order to provide ready access to any targeted structural and stereochemical pattern.



Scheme 3.1: Examples of Pyrrolidine Containing Pharmaceuticals

We recently reported the first catalytic ring expansion of unactivated vinyl aziridines (**3.11**, Scheme 2.2) to 3-pyrrolines (**3.12**).[4] The substrate scope of this new transformation was shown to be quite broad for a range of tosyl and phthalimide protected vinyl aziridines,. In planning for evaluating the potential of this new method for accessing appropriately protected chiral vinyl aziridines[5] the union of an imine and suitably activated nucleophile seemed to be the optimal approach. The benefits of this net [2+1] disconnection include a convergent route, easy introduction of nitrogen protecting groups for evaluation, and most importantly the flexibility of either employing a chiral catalyst or a chiral auxiliary based approach. This retrosynthetic analysis is highlighted for chiral pyrrolidine **3.13**, which we envisioned would originate from the copper catalyzed ring expansion of a *trans*- or *cis*-vinyl aziridine (**3.14** and **3.15**). These isomeric vinyl aziridines could be accessed from imines **3.17** and **3.18** and nucleophiles **3.16** and **3.19** in which case either coupling partner could serve as the chiral auxiliary. Our analysis further concluded that chiral sulfonium species seemed most suitable for the task of serving as a chiral nucleophile (**3.16**), while chiral sulfinamides would best serve the role of a chiral electrohpile (**3.18**). The constitutional aziridine isomers of aziridines **3.14** and **3.15** are also viable precursors. These are less attractive from a synthetic perspective as their assembly doesn't rely on using components of similar complexity and their ring expansion would need to be perfectly stereoselective.

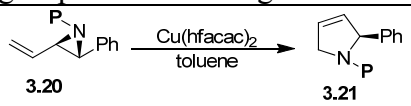


Scheme 3.2: Retrosynthetic Analysis for Chiral Pyrrolidines

3.2 Results and Discussion

Before starting to assemble the requisite chiral aziridines needed for our studies, we felt it was of critical importance to learn if other nitrogen protecting groups beyond Ts and NPhth were compatible where a suitable match for this new reaction. A priori, we realized that aryl and acyl groups would be particularly challenging, given their known tendency to undergo Claisen rearrangements[6] or intramolecular displacement reactions.[7] Our studies revealed that alkyl, aryl, and amide nitrogen protecting groups were incompatible with the reaction conditions and did not afford any 3-pyrroline products (Table 3.1). Interestingly, Boc protected aziridine (entry e) did ring expand to the desired 3-pyrroline with no detectable amounts of other heterocycles. When these results are evaluated in the context of our retrosynthetic goals for constructing chiral vinyl aziridine substrates and available reliable asymmetric aziridine methods it became evident that sulfonamides would best serve our cause. We therefore focused our efforts on evaluating a range of useful sulfonamide protecting groups (entries g-h) that would provide users of this methodology with choices that would best fit their synthetic task. We were delighted to learn that Ns and Bus sulfonamide groups, in addition to *p*-toluenesulfonamide (entry a), were compatible with the ring expansion conditions. Curiously, *t*-butyl sulfinamide protected aziridine (**3.20f**) failed and instead of affording 3-pyrroline **3.21f** it formed (E)-1-phenyl butadiene in high yield.

Table 3.1: Ring Expansion – Nitrogen Substituent Tolerance

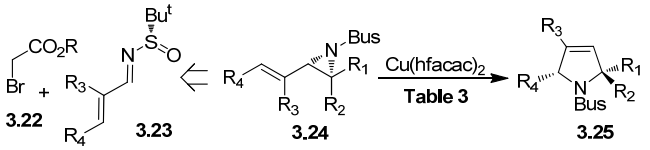


3.20 3.21

entry	Abbreviation	**P**	Time (h)	Yield of **3.21**	Other Products
a	Ts	*p*-toluenesulfonyl	5	92%	-
b[a]	NPhth	phthalimide[b]	2	97%	-
c[a]	Ph	phenyl	2	0%[c]	Mixture[8]
d[a]	Bn[a]	benzyl	2	0%	*(Z)-N*-benzylidene-1-phenylbut-2-en-1-amine isolated (86%)[9]
e	Boc	*tert*-butoxycarbonyl	5	60%	-
f	S(O)^{t}Bu	*tert*-butylsulfinyl	1	0%	*(E)*-buta-1,3-dien-1-ylbenzene (69%)
g	Bus	*tert*-butylsulfonyl	5	86%	-
h	Ns	*p*-nitrobenzenesulfonyl	5	94%	-
i	H	-	2	0%	Polymer
j	Bz	benzoyl	5	0%	Heine Reaction Products (50%)[10]

Conditions: 5% $Cu(hfacac)_2$,150°C a) racemic, b) *syn/anti* mixture of rotamers.

The remarkable success of proline derivatives as organocatalysts, [11] pharmaceuticals (Scheme 3.1), and natural products[12] ensures its status as a privileged structural motif. Chiral proline derivatives commonly originate from natural 3-hydroxy proline. This neglected family of chiral proline products seemed like a perfect application of our new methodology. Retrosynthetic analysis for **3.25** (Scheme 3.3) reveals that an optimal chiral vinyl aziridine ring expansion substrate (**3.24**) could originate from either a Darzens reaction[13] between a bromo acetate (**3.22**) and a chiral conjugated Ellman[14] imine (**3.23**) or alternatively from allyl sulfonium addition to a chiral glyoxalate imine.[15] With many bromoacetates commercially available, imine **3.13** being more stable than its glyoxolate counterpart, and an operationally more simple reaction the Darzens disconnection was clearly a better fit. In order to better understand the scope of the ring expansion, the resulting *cis*- and *trans*-vinyl aziridines were separated and evaluated individually.

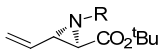
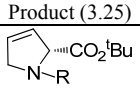
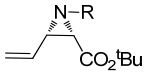
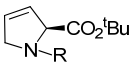
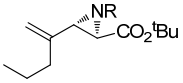
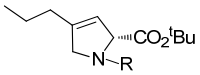
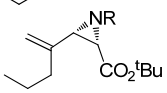
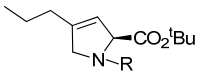
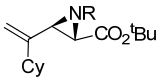
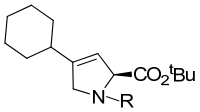
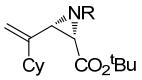
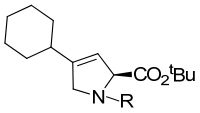
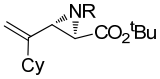
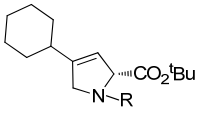
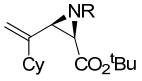
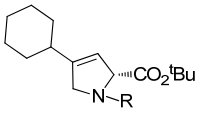
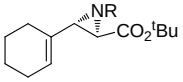
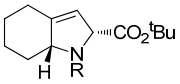
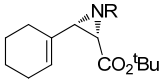
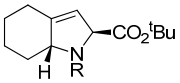
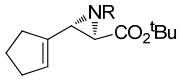
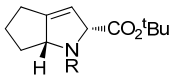
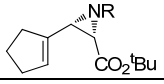
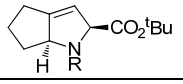


3.22 3.23 3.24 3.25

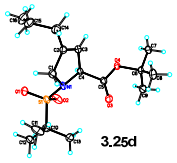
Scheme 3.3: Darzen Reaction Route to Chiral Proline Products

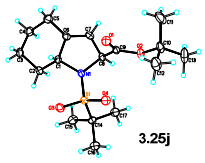
With a scaleable asymmetric route in hand we were able to assess the scope and ring expansion capabilities of chiral *Bus*-protected vinyl aziridines. The twelve chiral aziridines substrates shown in Table 3.2 (R = Bus) were accessed using the strategy detailed above. These chiral 3-pyrroline products match the cores of many of the pharmaceutical proline based angiotensin-converting enzymes and dipeptityl peptidase-4 inhibitors introduced in Scheme 3.1. Both *cis*- and *trans*-vinyl aziridines ring expand in excellent yields in the presence of catalytic amounts of $Cu(hfacac)_2$ to 3-pyrrolines. Entries e-h are an instructive reminder of the synthetic choices our catalytic ring expansion reaction offers. In accessing either enantiomer of the fosinopril core there are two suitable choices for each (entries e & f for desired configuration and g & h for the enantiomer). Entries i-l are particularly noteworthy because they demonstrate how control of the 2,5-pyrroline subsitution pattern can be controlled by starting with either a *cis*- or *trans*-aziridine. For the examples shown, the products could be advanced to the pharmaceutical cores of ramipril and perindopril. Entry l is an exception as this highly congested system scrambled prior to ring expansion. The absolute configuration of the pyrroline products of entries d, j, and l was established using X-ray crystallography.

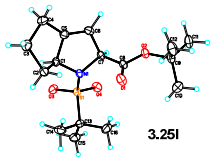
Table 3.2: Synthesis of Proline Based Pharmaceutical Building Blocks

Entry	Substrate (3.24)	Product (3.25)	Yield (%)
a			72
b			77
c			87
d			86
e			90
f			84
g			81
h			83
i			67
j			87
k			59
l			50

Conditions: 5% $Cu(hfacac)_2$, toluene, 5h, 150°C. Cy=cyclohexyl. R = Bus (**3.24 a-l**) R = $S(O)^tBu$ (**3.26 a-l**).

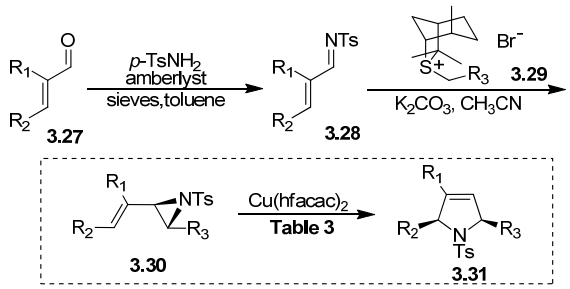






A complementary approach to the sulfonium strategy for accessing chiral vinyl aziridines *en route* to 3-pyrroline products is to use a chiral sulfide in place of a chiral imine. Although currently less developed than the excellent work of Ellman and Davis this strategy would alleviate additional oxidation step prior to ring expansion. In

pursuing this alternative starting material assembly strategy we turned our attention to the work of Aggarwal[16] and coworkers who have shown that chiral sulfonium nucleophiles can be used to access aziridines in a highly selective manner. To access the requisite chiral vinyl aziridines (**3.30**, Scheme 3.4) we choose to use his recently disclosed limonene based auxiliary (**3.29**)[17] for additions to sulfonamide imines (**3.28**). This scaleable two step asymmetric sequence provided chiral ring expansion precursors (**3.30**) in excellent yield.

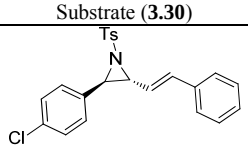
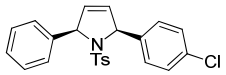
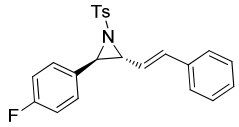
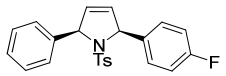
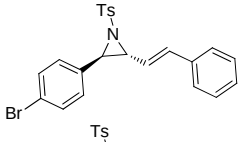
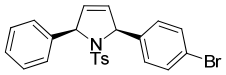
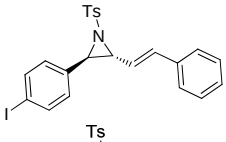
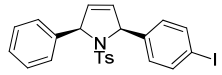
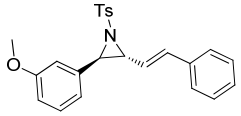
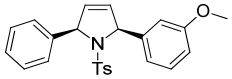
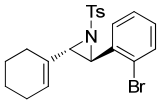
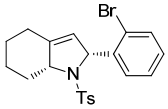
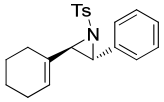
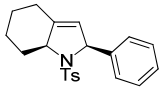
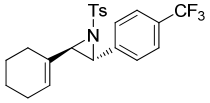
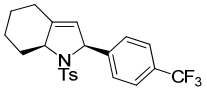
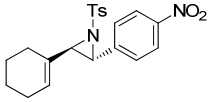
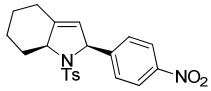
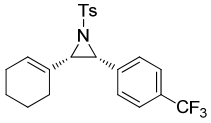
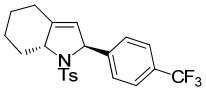
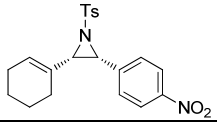
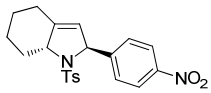


Scheme 3.4: Asymmetric Synthesis of Tosyl-Protected Vinylaziridines

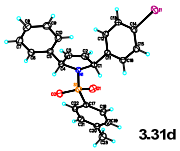
Chiral 2-aryl-substituted pyrrolidines are important structures that have received increased attention in recent years.[18] By accessing chiral 3-pyrrolines instead of pyrrolidines directly, our asymmetric route provides a double bond handle for further functionalization in a substrate controlled manner. We were delighted to learn that a large range of vinyl aziridine substrates could be ring expanded stereselectively using $Cu(hfacac)_2$ in uniformly excellent yields to their corresponding 2-aryl-3-pyrrolines (Table 3.3). In all cases, a single stereoisomer is obtained. Both donating and electron withdrawing substitutents are well tolerated, including aryl bromides, chlorides, iodides, and fluorides. The broad tolerance should serve those researchers interested in applying this new methodology to novel complex natural product, pharmaceutical, or organocatalytic architectures. Impressively, the corresponding chiral *cis*-vinyl aziridines stereoselectively afford the *trans*-fused 3-pyrroline products

(entries j and k). The absolute configuration of the pyrroline product of entry d was firmly established using X-ray crystallography.

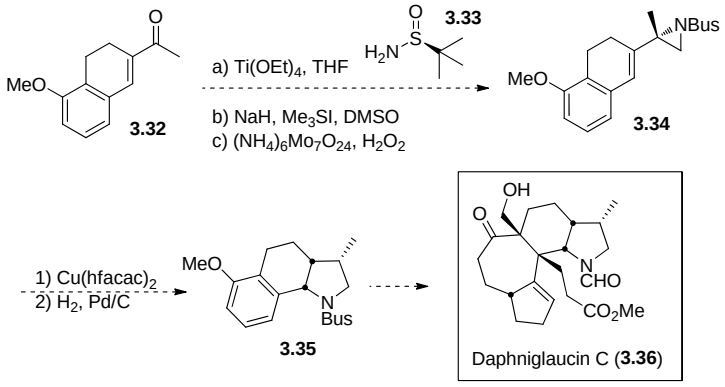
Table 3.3: Ring Expansion of Aryl Substituted Chiral Vinylaziridines

Entry	Substrate (**3.30**)	Product (**3.31**)	t (h)	Yield (%)
a			2	84
b			2	91
c			2	92
d			2	87
e			2	81
f			2	97
g			2	92
h			2	93
i			5	96
j			4	92
k			5	71

Conditions: 5% $Cu(hfacac)_2$, toluene, 150°C.



Daphniglaucin C (**3.36**), a relatively new member of the daphniphyllium alkaloid family, has been demonstrated to show promising tubulin polymerization inhibitory activity (Scheme 3.5) and as such a potential anticancer agent.[19] Its octahydro indole core containing five stereocenters seemed like a perfect fit for both demonstrating the use of the chiral method that is the focus of this work.[20] Towards that end we envisioned using known enone **3.32** to access a sulfonamide imine using $Ti(OEt)_4$ and then transformation to the aziridine using Corey-Chaykovsky conditions. The resulting aziridine would be oxidized using ammonium molybdate tetrahydrate as we have demonstrated in the synthesis of the substrates in Table 3.2. This cheap, practical, and simple oxidation protocol, which is commonly employed for accessing Julia olefination substrates,[21] has not been reported previously for converting sulfinamides to sulfonamides (**3.34**). With the exception of *m*-CPBA other commonly used oxidants were inferior to this practical protocol. We expect the rearrangement of aziridine **3.34** to proceed stereoselectively and the resulting 3-pyrroline can be reduced in the presence of hydrogen and palladium to afford the desired chiral octahydro indole core **3.35** of daphniglaucin C in only five steps from **3.32**. Dearomatization of the phenolic methyl ether, followed by ring expansion and a substrate controlled cycloaddition are envisioned for advancing **3.35** to daphniglaucin C (**3.36**).



Scheme 3.5**:** Asymmetric Approach Towards Daphniglaucin C

In summary, we have demonstrated new, practical, and complimentary routes to access valuable chiral 3-pyrroline products. This was accomplished by coupling an imine with the appropriate nucleophile and then catalytically ring expanding the resulting chiral vinyl aziridine using $Cu(hfacac)_2$. The substrate scope and functional group tolerance of this asymmetric pyrroline approach is very broad and the resulting products provide diverse opportunities for further functionalization. Given the importance and common occurrence of chiral pyrrolidines as cores of natural products, pharmaceuticals and organocatalysts this new strategy is expected to find wide use.

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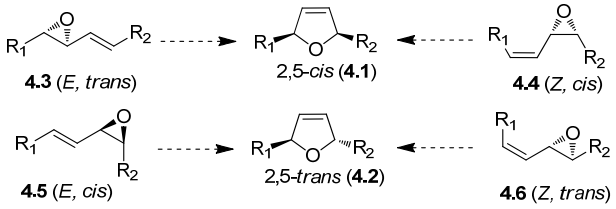
Chapter 4

Stereoselective Ring Expansion of Vinyl Oxiranes. Mechanistic Insights and Natural Product Total Synthesis

4.1 Background and Significance

The central part of our research program is the development of broadly applicable atom-efficient synthetic methods to generate structural complexity. We recently reported a new copper-catalyzed ring expansion of vinyl oxiranes using commercially available, structurally simple, and air stable copper(II) catalysts.[1] These studies demonstrated the success of this reaction for a broad range of substrates. Missing from these early studies were experiments focused on assessing the stereoselective potential of the ring expansion. The studies presented herein are aimed at addressing this point and to learn if the oxirane C-O bond that is broken during the ring expansion could be stereoselectively transferred to the olefin terminus. Moreover, an added benefit to the proposed studies would be critical mechanistic insights that could shed further light on the exact mechanism of this unique catalytic ring expansion reaction. If vinyl oxiranes can indeed be stereoselectivity ring expanded using copper catalysts then the practical benefits of this new reaction would be significantly expanded. Also this transformation would rival existing methods[2] to stereoselectively access 2,5-dihydrofurans in terms of efficiency and scope.



Scheme 4.1: Stereoselective Vinyl Oxirane Ring Expansions

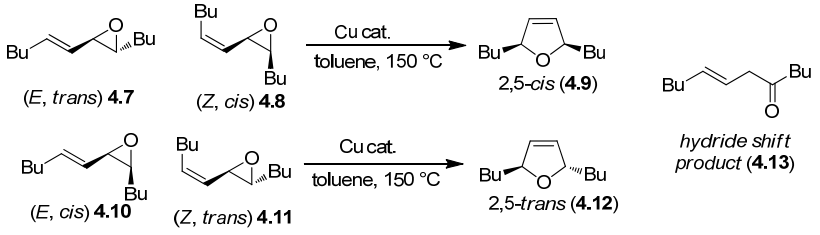
Our studies have focused on disubstituted vinyl oxirane substrates (Scheme 4.1), which depending on their stereochemistry and olefin geometry could serve as precursors for accessing either a 2,5-*cis*- or a 2,5-*trans*- substituted 2,5-dihydrofuran product. In the case of a stereoselective ring expansion, vinyl oxiranes **4.3** and **4.4** would be expected to afford the *cis*-product (**4.1**) while **4.5** and **4.6** should similary

afford the *trans*-product (**4.2**). When these substrates are ranked with respect to steric crowding during formation of the new C-O bond, vinyl oxiranes **4.3** and **4.5** emerge as more suitable precursors for accessing the 2,5-*cis*- and 2,5-*trans* dihydrofuran products respectively.

4.2 Results and Discussion

Therefore we synthesized vinyl oxiranes **4.7** and **4.11**,[3] which differ only in the oxirane stereochemistry (*trans* or *cis* substituted oxiranes). Ring expansion of these two substrates afforded symmetrically substituted *cis*- and *trans*-dihydrofurans **4.9** and **4.12** (Table 4.1). Under the standard reaction conditions used in our previous paper (entries 5 and 16) we were able to obtain both dihydrofurans in good diastereomeric purity, but with low chemical yield due to the formation of byproduct (**4.13**). Reaction optimization revealed that the success relied most strongly on the temperature and appropriate catalyst loading. After thorough optimization we were delighted to learn that dihydrofuran products **4.9** and **4.12** could be obtained with high levels of stereoselectivity and good chemical yield (entries 7 and 18). In general we observe that both a lower catalyst loading and slow addition of the catalyst improves the yield (chemoselectivity) of the product. These results establish for the first time that vinyl oxiranes can be stereoselectively ring expanded to 2,5-dihydrofurans.[4]

Table 4.1: Stereoselective Synthesis of Dihydrofurans **4.9** and **4.12**



Entry	Oxirane	Cu. Cat	Cat. (mol%)	Time (h)	Chemosel. (**4.9**+**4.12**):**4.13**	Stereosel. **4.9**:**4.12**	Yield %[a]
1	**4.7**	$Cu(acac)_2$	5	15	1:!	3:1	38
2	**4.7**	$Cu(tfacac)_2$	5	15	9:1	6:1	77%
3	**4.7**	$Cu(FOD)_2$	5	15	10:1	12:1	84 (71)
4	**4.7**	$Cu(hfacac)_2$	10	15	1 : 1	10 : 1	45
5	**4.7**	$Cu(hfacac)_2$	5	1	3 : 1	11 : 1	69
6	**4.7**	$Cu(hfacac)_2$	1	6	3 : 1	>20:1	75 (70)
7	**4.7**	**$Cu(hfacac)_2$**	**5**[b]	**8**	**11 : 1**	**15 : 1**	**86 (79)**
8	**4.8**	$Cu(acac)_2$	5	15	-	-	0
9	**4.8**	$Cu(tfacac)_2$	5	15	-	-	0
10	**4.8**	$Cu(hfacac)_2$	5	15	1.5:1	2:1	38
11	**4.8**	$Cu(hfacac)_2$	1	40	1:1	3.5:1	41 (24)
12	**4.8**	$Cu(hfacac)_2$	5[c]	12	6:1	3:1	63
13	**4.10**	$Cu(acac)_2$	5	15	1.5:1	1:8	50
14	**4.10**	$Cu(tfacac)_2$	5	15	5:1	1:10	75
15	**4.10**	$Cu(hfacac)_2$	10	1	1 : 7	1 : 10	11
16	**4.10**	$Cu(hfacac)_2$	5	2	2 : 1	1 : 12	62
17	**4.10**	$Cu(hfacac)_2$	1	15	1 : 1	1 : 8	44
18[d]	**4.10**	**$Cu(hfacac)_2$**	**5**	**3**	**2.5 : 1**	**1 : 18**	**68 (66)**
19	**4.11**	$Cu(acac)_2$	5	15	1:2	1:1	17
20	**4.11**	$Cu(tfacac)_2$	5	15	2:1	2:1	21
21	**4.11**	$Cu(hfacac)_2$	5	15	5:1	1:1	40
22	**4.11**	$Cu(hfacac)_2$	1	15	12:1	2:1	33

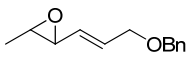
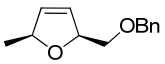
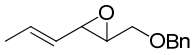
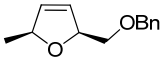
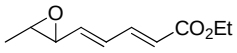
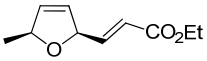
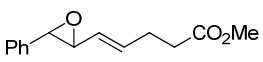
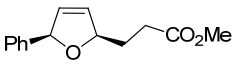
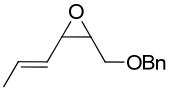
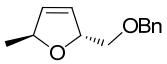
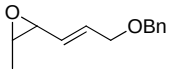
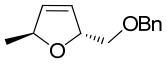
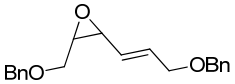
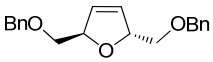
a) Estimated by NMR (isolated yield), b) Added via syringe pump (1.25 mol%/hour for 4 hours). c) Added via syringe pump (0.6 mol%/hour for 8 hours). d) 0.13 M in benzene.

These results are even more profound when one considers the stability of reactants and products. DFT calculations (B3LYP/6-311+G(d,p)) on **4.7-4.13** revealed that vinyl oxiranes **4.7** and **4.10** are very similar in energy. Closer examination reveals that oxirane **4.7** (0.0 kcal/mol) forms the less stable *cis*-product **4.9** (-13.7 kcal/mol) while oxirane **4.10** (1.1 kcal/mol) affords the preferred *trans*-product **4.12** (-13.9 kcal/mol). Both dihydrofuran products **4.9** and **4.12** are less stable than the byproduct

4.13 (-27.1 kcal/mol) formed in the reaction. These energy relationships strongly discredit a mechanism involving a carbocation intermediate.

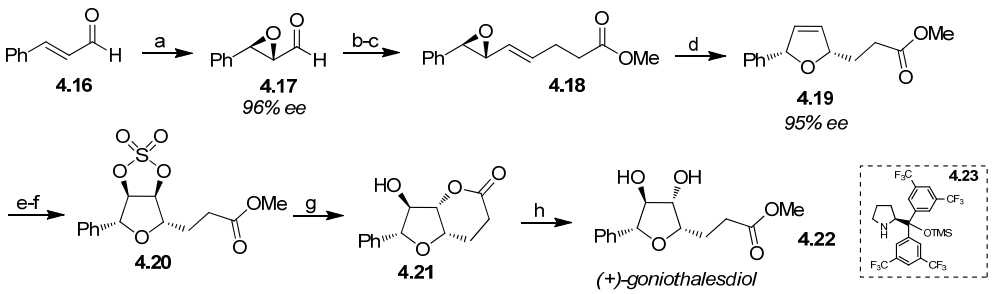
We have expanded our studies to include the seven additional examples presented in Table 4.2. Our results are in agreement with what we learned from the ring expansion of vinyl oxiranes **4.7** and **4.10**, wherein high selectivity was achieved by lowering the catalyst loading. As expected, *cis*-2,5-dihydrofuran products (**4.15a-4.15d**) were stereoselectively obtained from (*trans,E*)-vinyl oxirane precursors (**4.14a-**4**.14d**), while *trans*-2,5-dihydrofuran products (**4.15e-4.15g**) were accessed by ring expanding (*cis,E*)-vinyl oxirane substrates (**4.14e-4.14g**). Both isolated yields and stereoselectivity are excellent for all substrates. Functional groups such as ethers, esters, enoates, and aryl groups are well tolerated. These new stereoselective results allow strategic design of routes to either *cis*- or *trans*- 2,5-dihydrofuran targets by employing the appropriate vinyl oxirane precursor.

Table 4.2: Stereoselective Ring Expansion of Vinyl Oxiranes

Entry	Starting Material (**4.14**)	Product (± **4.15**)	Yield (cis : trans)
a			94%[a,b] (>20:1)
b			88%[a,b] (13:1)
c			84%[a,c] (8:1)
d			70%[a,d] (8:1)
e			92%[e,f] (1:6)
f			96%[f,g] (1:8)
g			93%[f] (1:7)

Conditions: 5 mol% $Cu(hfacac)_2$ in toluene at 150 °C. a) Isolated yield of diastereomerically pure material b) Added via syringe pump (0.6 mol%/hour for 8 hours) c) 2 mol % added via syringe pump (0.11 mol%/hour for 17 hours) d) Added via syringe pump (2.5 mol%/hour for 2 hours) e) 100 °C f) Isolated yield of both diastereomers g) benzene.

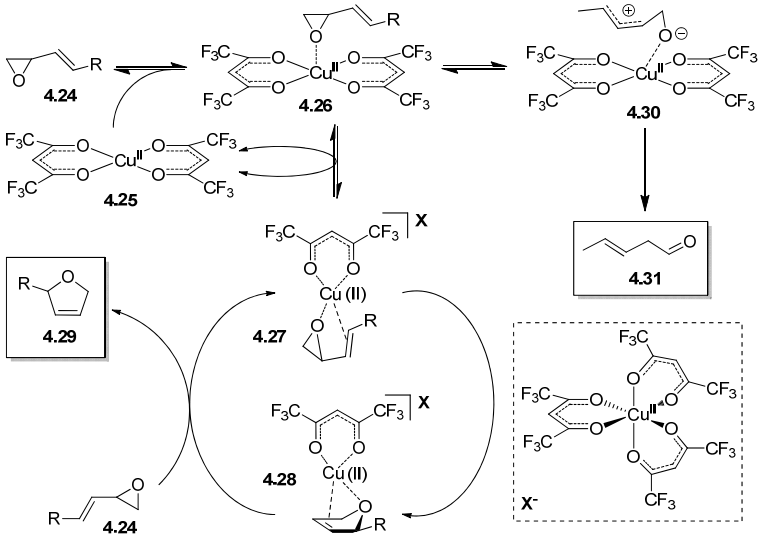
The anti-cancer agent goniothalesdiol[5] (Scheme 4.2) was chosen as a target for assessing the value of the new stereoselective copper catalyzed ring expansion protocol and to showcase it using an enantiopure oxirane substrate. Goniothalesdiol, a densely functionalized tetrahydrofuran based structure, seemed like a perfect target for this task. Towards that end, cinnamaldehyde (**4.16**) was converted to chiral epoxy aldehyde **4.17** using Jorgensen's asymmetric organocatalytic epoxidation protocol.[6] Treatment of **4.17** with vinyl magnesium bromide followed by a Johnson-Claisen rearrangement[7] of the resulting allylic alcohol efficiently formed vinyl oxirane **4.18** as a single (E)-olefin isomer. The copper-catalyzed rearrangement of this chiral oxirane afforded *cis*-2,5-dihydrofuran **4.19** in 70% yield and excellent enantiopurity after separation from the *trans*-diastereomer. Substrate controlled epoxidation of dihydrofuan **4.19** was expected to give an epoxide that could be opened in an intramolecular fashion to lactone **4.21**.[8] Surprisingly, epoxidation of **4.19** proved troublesome, affording only the corresponding furan. This problem was solved by constructing a cyclic sulfate instead of an epoxide. Sharpless has shown that these reactive synthons can be obtained from vicinal hydroxyl groups.[9] Dihydroxylation of **4.19** selectively afforded 4-*epi*-goniothalesdiol in high yield. Upon treatment of this diol with thionyl chloride and ruthenium tetroxide, cyclic sulfate **4.20** was obtained. This activated diol was efficiently opened in an intramolecular fashion to lactone **4.21**.[10] Opening of the lactone with Amberlyst-15 in methanol afforded goniothalesdiol in only eight steps from cinnamaldehyde. This short asymmetric synthesis of goniothalesdiol is a testament to the value of our new stereoselective ring expansion protocol.



Scheme 4.2: Asymmetric Total Synthesis of Goniothalesdiol

Reagents and Conditions. a) H_2O_2, **4.23**, 80%; b) CH_2=$CHMgBr$, 47%; c) $CH_3C(OMe)_3$, cat. propionic acid, 83%; d) 5 mol% $Cu(hfacac)_2$, toluene, 150°C, 70%; e) cat. OsO_4, NMO, acetone, H_2O, 99%; f) $SOCl_2$, Et_3N then $NaIO_4$, $RuCl_3$•$3H_2O$, CH_3CN, H_2O, 88%; g) 15% H_2SO_4, THF, 65°C, 87%; h) Amberlyst-15, MeOH, 99%. NMO = N-methylmorpholine-N-oxide.

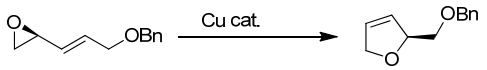
Detailed kinetic studies of the rearrangement of vinyl oxirane **4.7** revealed a sigmoidal curve for the formation of dihydrofuran product **4.9**, which is in perfect agreement with our studies of vinylaziridines.[1c] When similar kinetic analyses for *cis*-vinyl oxirane substrate **4.10** are performed, the same general observations are made, with the added insight that formation and disappearance of small amounts of *trans*-vinyl oxirane **4.7** can also be observed in the kinetic trace. This suggests that the active catalyst accommodates oxirane isomerization while suppressing the otherwise detrimental hydride shift pathway (also observed for **4.14e-4.14g**). Based on our data, the catalytic cycle shown in Scheme 4.3 is proposed.



Scheme 4.3: Proposed Catalytic Cycle

The kinetic data seem to suggest that following an induction period a more active catalyst is formed, which then proceeds to stereoselectively ring expand vinyl oxiranes. We envision that $Cu(hfacac)_2$ (**4.25**) reversibly coordinates to the oxirane (**4.24**) lone pair thus forming substrate-catalyst complex **4.26**. This complex may react with another $Cu(hfacac)_2$ (**4.24**) and be transformed to chelated substrate bound cationic copper(II) complex **4.27**, wherein $Cu(hfacac)_3^-$ serves as the non-nucleophilic counterion ($\mathbf{X}^-$).[11] This cationic catalyst acts as the optimal Lewis acid that holds the substrate together in such a way that the chirality of C-O bond is transferred (without scrambling) to the olefin terminus to form dihydrofuran bound copper complex **4.28**. Simple ligand exchange releases **4.29** and coordinates another vinyl oxirane (**4.24**). This release results in the formation of **4.27** and completesthe first round of the catalytic cycle. We further propose that the competing hydride shift product (**4.31**) is formed from copper complex **4.30**, wherein the C-O oxirane bond has already been broken. An equilibrium arrow is placed between catalyst-substrate complexes **4.26** and **4.30** based on the kinetic data obtained for vinyl oxirane **4.10** as discussed above. Cu(I) mechanistic proposals do not seem to match our data. Copper (I) (hfacac)(BTMSA) is the only Cu(I) catalyst that we have shown can ring expand vinyl oxiranes, which is because it disproportionates under the reaction conditions to the active catalyst, $Cu(hfacac)_2$, and Cu^0. This fact is commonly exploited in the field of chemical vapor deposition (CVD), wherein fluorinated acetylacetonate copper catalysts are routinely employed. Neither spectroscopic data or *in situ* reduction experiments of $Cu(hfacac)_2$ using classic reducing agents such as cobaltocene, hydrazine, or AIBN support a Cu(I) mechanism.[12]

Table 4.3: Stereoselective Ring Expansion of Vinyl Oxirane **4.32**



4.32 **4.33**

Entry	Cu cat.	Mol %	T °C	Solvent	ee (%)[a]
1	$Cu(hfacac)_2$	10	150	Toluene	61
2	$Cu(hfacac)_2$	5	150	Toluene	63
3	$Cu(hfacac)_2$	2.5	150	Toluene	72
4	$Cu(hfacac)_2$	1	150	Toluene	73
5	$Cu(hfacac)_2$	0.5	150	Toluene	77[b]
6	$Cu(hfacac)_2$	1	125	Pentane	20
7	$Cu(hfacac)_2$	1	150	Benzene	77
8	$Cu(hfacac)_2$	1	150	Fluorobenzene	78
9	$Cu(hfacac)_2$	1	150	Hexafluorobenzene	56
10	$Cu(hfacac)_2$	1	125	Toluene	78
11	$Cu(hfacac)_2$	1	175	Toluene	81
12	$Cu(hfacac)_2$	1	200	Toluene	79
13	$Cu(acac)_2$	5	150	Toluene	14
14	$Cu(tfacac)_2$	5	150	Toluene	15
15	$Cu(FOD)_2$	5	150	Toluene	23
16	Cu(hfacac)BTMSA	5	150	Toluene	80
17	$Cu(hfacac)_2$	1	150	Toluene (0.05 M)	66
18	$Cu(hfacac)_2$	1	150	Toluene (0.20 M)	62
19	$Cu(hfacac)_2$	1	150	Toluene (0.40 M)	60
20	**$Cu(hfacac)_2$**	**0.5**	**175**	**Fluorobenzene**	**92**[c,d]

Conditions: Cu cat. at 0.1M for 15 hours a) The ee for 4.33 was determined by chiral HPLC, b) 45 hours, c) 24 hours d) 60% isolated yield.

Challenging the reaction further we decided to evaluate if chiral mono substituted vinyl oxirane substrates such as **4.32**[13] could be ring expanded to dihydrofuran **4.33**[14] without any stereochemical scrambling. First, the product (**4.33**) was determined not to epimerize under the reaction conditions as is necessary for success. As is evident from entries 1-5 the $Cu(hfacac)_2$ catalyst loading impacts the stereoselectivity of the reaction, with 0.5 mol% being optimal. This increase in enantioselectivity with a decrease in catalyst loading, although rare, is not without precedence for metal-catalyzed reactions.[15] We decided to evaluate how changing the solvent would impact stereoselectivity. When the standard toluene (entry 4) conditions are compared to entries 6-9 it was determined that hexafluorobenzene negatively

impacts stereoselectively, pentane almost completely erodes it, while benzene and fluorobenzene are on par with toluene. The ring expansion can be done at several different temperatures with very comparable stereochemical outcomes (entries 10-12). Likewise, the concentration of the reaction does not have a dramatic impact on the chirality transfer so the standard 0.1 M was used. Lastly, the electronics of the catalyst are crucial to success in the rearrangement with the more electrophilic Cu (II) catalysts being superior. When this data is analyzed and put together (entries 5, 8, and 11), the result was excellent affording dihydrofuran product **4.33** in 92% ee (entry 20).

In summary, we have demonstrated that this new copper catalyzed vinyl oxirane ring expansion can be performed stereoselectively, therein providing access to *cis*- or *trans*-products simply by starting with the matching oxirane precursor. Similarly we have demonstrated that chiral 2-substituted dihydrofuran products of high optical purity can also be obtained. We propose that the active catalyst for the ring expansion is an *in situ* generated cationic copper(II) catalyst. These results were utilized to accomplish the shortest asymmetric synthesis of the natural product goniothalesdiol, highlighting the powerful retrosynthetic option this new catalytic synthetic method offers.

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(10) Lactone **4.21** has previously been prepared and completes the formal synthesis of (+)-Altholactone (Somfai, P. *Tetrahedron* **1994**, *50*, 11315-11320) and (-)-Etharvensin (Bermejo, A.; Blazquez, M. A.; Serrano, A.; Zafra-Polo, M. C.; Cortes, D.*J. Nat. Prod.* **1997**, *60*, 1338-1340).

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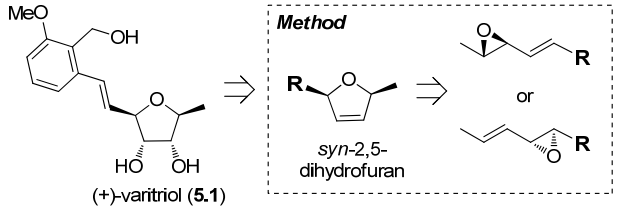
Chapter 5

The Strategic Marriage of Method and Motif. Total Synthesis of Varitriol

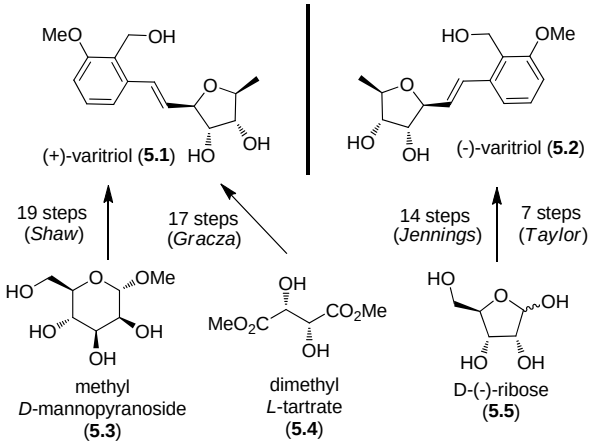
5.1 Background and Significance

The marine natural product varitriol (**5.1** Scheme 5.1) was recently isolated and characterized.[1] Screening of varitriol against the National Cancer Institute 60-cell line *in vitro* panel revealed promising activity against a number of important types of cancer. This anti-cancer activity, coupled with varitriol's tetrahydrofuran core, constitutes an opportunity to showcase our new copper-catalyzed vinyl oxirane ring expansion reaction (the "method")[2] in an application to varitriol (the "motif").[3] Of course, this success depends on the judicious choice of substituents (R=?), source material and well matched accompanying reactions. The studies presented herein are aimed at identifying the most suitable vinyl oxirane substrates for accessing varitriol.



Scheme 5.1: Motif (Varitriol) and Method (Vinyl Oxirane Ring Expansion)

Not surprisingly, given varitriol's attractive biological profile it has garnered the attention of synthetic chemists. Four syntheses of varitriol (**5.1**)[4] and its enantiomer (**5.2**)[5] have been completed to date (Scheme 5.2).[6,7] Interestingly, all these approaches have utilized chiral pool source materials. With the exception of Taylor's synthesis of **5.2**, the longest linear sequences seems excessive for a molecule of varitriol's complexity. Our approach focuses on the rapid synthesis of the dihydrofuran core from non-chiral pool starting materials[8] with minimal use of protecting groups[9] or redox adjustments.[10]

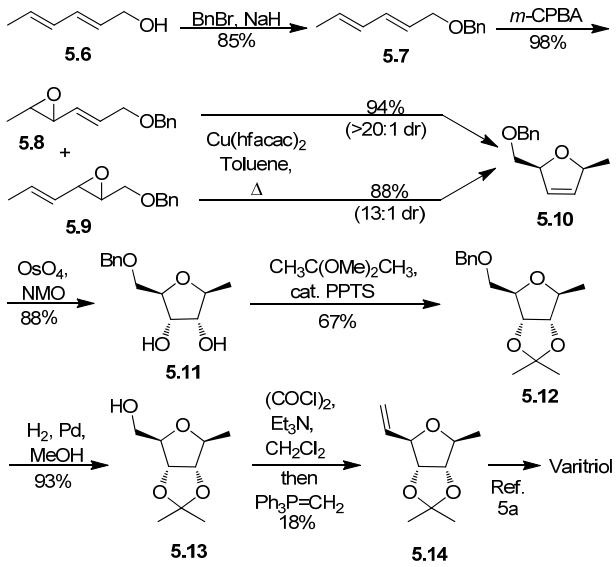


Scheme 5.2: Chiral Pool Total Syntheses of (+)- and (-)-Varitriol

5.2 Results and Discussion

Our synthetic efforts commenced with epoxidation of benzyl protected dienyl alcohol **5.7** (Scheme 5.). The two regioisomeric vinyl oxiranes (**5.8** and **5.9**) were separated and subjected to the copper-catalyzed rearrangement conditions. Using $Cu(hfacac)_2$, both vinyl oxiranes rearranged to form the expected *cis*-2,5- dihydrofuran **5.10** in excellent yield and with high stereoselectivity.[3] Substrate controlled dihydroxylation (**5.11**) installed the natural product's other two stereocenters. At this point in the synthesis, the *cis*-diol was protected as an acetonide (**5.12**) and the benzyl protecting group of the primary alcohol removed by hydrogenolysis. Oxidation of the free alcohol (**5.13**) afforded an aldehyde, which was immediately subjected to a Wittig olefination reaction. Tetrahydrofuran product **5.14** is a known synthetic intermediate in a recently completed synthesis of varitriol by Jennings and coworkers.[5a] This new synthetic approach allowed us to access **5.14** in eight steps from dienol **5.6**, which is four steps shorter than the earlier route from *D*-ribose. It is important to note in comparing the two sequences that our new route has not been executed using chiral starting materials. Literature examples support the notion that our new synthetic sequence lends itself well to established asymmetric epoxidation protocols. For example, Somfai[11] has demonstrated that **5.7** can be oxidized to (*2R*,*3R*)-**5.8** in good

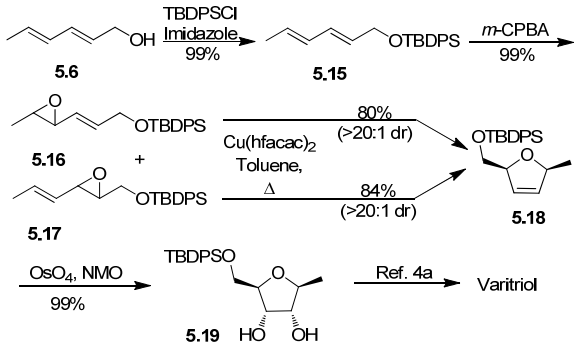
yield and 95% *ee* using one of Yian Shi's chiral diooxirane reagents. Advancing this product would provide access to (-)-varitriol (**5.2**). Interestingly, Shi has demonstrated that when TBS-protected **5.15** is oxidized, a mixture of (*2R*,*3R*)- and (*4R*,*5R*)-epoxides are produced, with the latter being a perfect match with our method to access (+)-varitriol (**5.1**).[12]



Scheme 5.3: Formal Synthesis of Varitriol (First Approach)

In the total syntheis of natural (+)-varitriol (**5.1**) by Shaw and coworkers,[4a] protected triol **5.19** (Scheme 5.4) served as a key intermediate. Our stereoselective vinyl oxirane ring expansion strategy seemed well-suited for accessing **5.18** and further evaluating the functional group compatibility of our methodology. Furthermore, we hoped to develop a better diol protecting group, as the aldehyde obtained from **5.13** performed very poorly in the Wittig reaction.[4a,5a] Shaw demonstrated in his synthesis that this issue could be addressed by using PMB-protecting groups instead of an acetonide to mask the diol. Our synthetic route commenced with silyl protection of dienol **5.8**. The resulting diene was epoxidized to furnish vinyl oxiranes **5.16** and **5.17**, which were readily separable. Both oxiranes ring

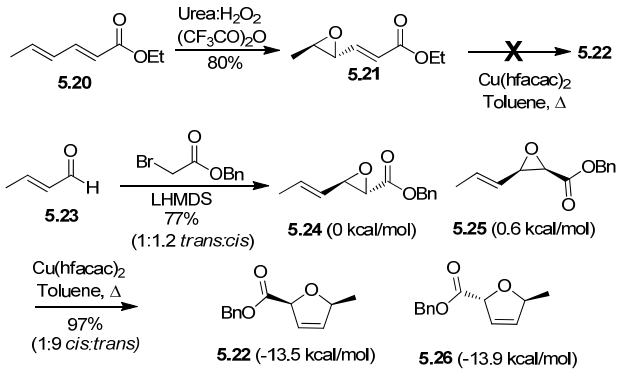
expanded efficiently in the presence of $Cu(hfacac)_2$ to produce *cis*-2,5-dihydrofuran **5.18** in excellent yield and better than 20:1 stereoselectivity. In concert with our goal of making the sequence as practical as possible, we have also successfully ring expanded the mixture of epoxides (**5.8**/**5.9** and **5.16**/**5.17**) obtained from the dienes **5.7** and **5.15** to 2,5-dihydrofurans **5.10** and **5.18**, thus eliminating the need to separate the two vinyl oxirane constitutional isomers. These ring expansions have been performed on gram scale. This result also establishes silyl group compatibility with our ring expansion conditions. Substrate controlled dihydroxylation using osmium tetroxide afforded **5.19** in only 4 steps from dienol **5.8**, which compares very favorably to Shaw's twelve step synthesis of **5.19** from methyl *D*-mannopyranoside.



Scheme 5.4: Formal Synthesis of Varitriol (Second Approach)

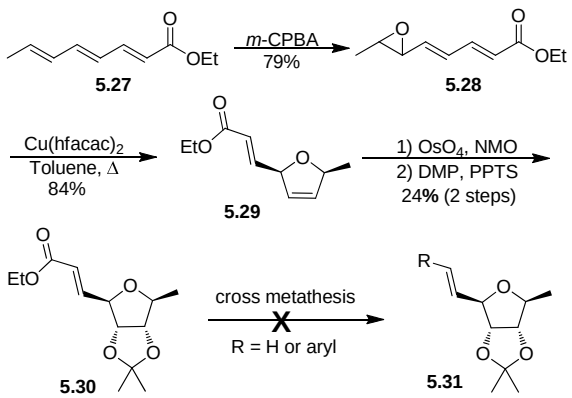
Although our new routes to these known synthetic intermediates are shorter than previous ones, they are not without room for improvements. In particular, there should be a way to bypass using a protecting group on the primary alcohol and thus truncate these routes by two more steps. Constitutional vinyl oxirane isomers **5.21** and **5.24** (Scheme 5.5), which can be accessed in a single step from **5.20**[13] and **5.23**[14] respectively, seemed to fit this goal perfectly. Moreover, the significant steric and electronic differences between **5.21** and **5.24** might provide us with further mechanistic insights. Interestingly, vinyl oxirane **5.21** decomposed instead of ring expanding to the expected 2,5-dihydrofuran product **5.22**, while its constitutional

isomers (**5.24**)[15] ring expanded nicely in high yield. From a mechanistic perspective, this result is interesting. If coordination of the copper catalyst is invoked for the mechanism of this reaction, then it is not too surprising that the acrylate olefin moiety of **5.21** would be far poorer olefin donor than the olefin of **5.24**. Interestingly, the equivalent aziridine substrate of **5.21** does successfully ring expand. We attribute this difference to the fact that the aziridine coordinates more effectively to the copper catalyst than the oxirane and also because of the competing hydride shift pathway the vinyl oxirane substrates need to overcome. [16] Upon further analysis, we learned that under the reaction conditions the *cis*-isomer (**5.22**) had epimerized to the thermodynamically more stable *trans*-isomer (**5.26**). Although, the epimerization of **5.22** to **5.26** precluded advancement of this product, this new route succeeded in avoiding the use of protecting groups to access a functionalized dihydrofuran product. The fact that a mixture of *cis*- and *trans*-oxiranes **5.24** and **5.25** ring expanded to form *trans*-2,5-dihydrofuran **5.26** as the main product in excellent yield is noteworthy. We have recently demonstrated that *trans-E*- and *cis-E*- vinyl oxiranes can be stereoselectively ring expanded to *syn*- and *anti*-2,5-dihydrofurans respectively. These studies did not uncover any epimerizations following ring expansion, but none of those substrates contained such an easily epimerizable group like the ester of vinyl oxirane **5.24**.



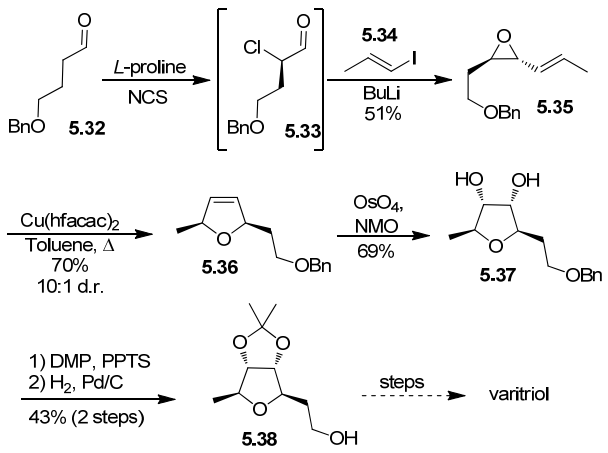
Scheme 5.5: Third Synthetic Approach towards Varitriol

Is there room for further improvement? Although this last route is very short, the union of the furan moiety and the aryl group would require a three step sequence of ester reduction, Wittig olefination, and cross metathesis. The simplest way to shave off one more step from this sequence would be to use a Wittig or Julia olefination instead of the cross metathesis reaction to join the two fragments. Alternatively, by using a substrate such as **5.27** (Scheme 5.6) that contains the desired exocyclic carbon atoms there was a possibility of saving three steps and providing access to varitriol in only four steps. Towards that end, commercially available triene **5.27** was selectively transformed to vinyl oxirane **5.28**, which upon treatment with $Cu(hfacac)_2$ ring expanded efficiently to the expected *cis*-2,5-dihydrofuran product **5.29**. Dihydroxylation of diene **5.29** affords a mixture of products that when protected yields acetonide **5.30**. This product is only a cross metathesis away from varitriol. At the outset, it was well understood that acrylate **5.30** was a poorly matched cross metathesis substrate. We have been able to find only one example in the literature wherein an acrylate group is exchanged for a terminal olefin. This was accomplished in modest yield using Grubbs second generation catalyst and ethylene.[17] Therefore it was not entirely surprising that we were unable to convert **5.30** to **5.31** using either ethylene or styrene derivatives. Determined to advance this highly desirable substrate, we also evaluated relay metathesis substrates[18] wherein the ethyl ester had been replaced with an appropriate allyl ester group but to no avail.



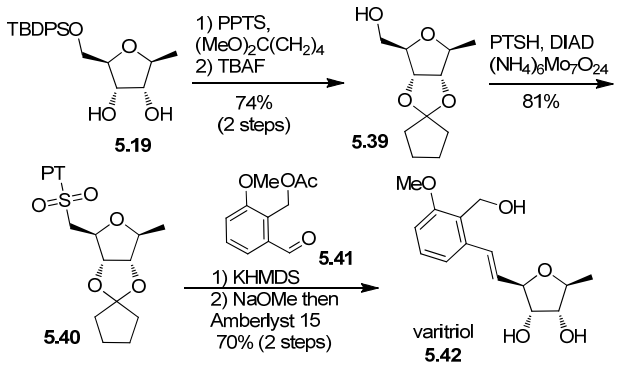
Scheme 5.6: Fourth Synthetic Approach towards Varitriol

Inspired by how convergently components were brought together by using the Darzen's reaction (Scheme 5.5) and a desire to access enantiopure vinyl oxirane starting materials, we decided to explore an alternative approach (Scheme 5.7). We argued that addition of an appropriate vinyl nucleophile to a chiral α-chloro aldehyde would expediently afford the desired chiral vinyl oxirane substrate. Towards that end, commercially available aldehyde **5.32** was chlorinated using Jorgensen's organocatalytic procedure[19] and the crude product subjected to vinyllithium reagent **5.34**[20] to afford vinyl oxirane **5.35**. Ring expansion of this vinyl oxirane provided *cis*-2,5-dihydrofuran product **5.36**, which was then dihydroxylated (**5.37**). The diol was protected as an acetonide and the benzyl ether was deprotected using palladium mediated hydrogenolysis to furnish **5.38** in only six steps from aldehyde **5.32**. Alcohol **5.38** is a versatile synthetic intermediate that could be dehydrated to afford cross metathesis substrate **5.14** (Scheme 5.3) without relying on the challenging olefination step. Alternatively, **5.38** could be oxidized to an aldehyde and then reacted with the appropriate aryl anion. The resulting secondary alcohol would then be dehydrated to afford varitriol.



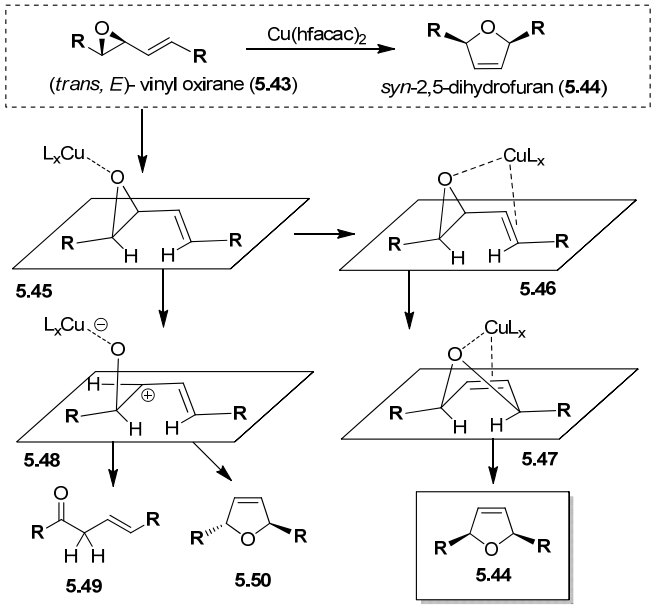
Scheme 5.7: Fifth Synthetic Approach towards Varitriol

In order to complete the synthesis of varitriol, we then decided to utilize readily available diol **5.19**. Protection of the diol in **5.19** as an acetal followed by treatment with tetrabutyl ammonium fluoride (TBAF) afforded **5.39**. A variety of sequences can be envisioned to convert primary alcohol **5.39** to varitriol, the most successful approach we found is depicted in Scheme 5.8. This involves a Mitsunobu reaction with 1-phenyl-1H-tetrazole-5-thiol (PTSH)[21] followed by *in situ* oxidation with ammonium molybdate tetrahydrate to give sulfone **5.40**. Julia olefination[22] with aldehyde **5.41** produced exclusively the *E*-olefin without any furan epimerization in high yield. The analogous Julia olefination with the sulfone and aldehyde moieties reversed was shown to be inferior due to poor yield and olefin selectivity. Deprotection of the olefination product afforded varitriol which matched previously reported data.



Scheme 5.8: Total Synthesis of Varitriol

What accounts for the excellent stereoselectivity of our copper catalyzed vinyl oxirane ring expansion reaction? We currently favor a chelation model to account for the observed success in stereoselectively ring expanding vinyl oxiranes (Scheme 5.9). We have previously shown that *trans*- and *cis*- *E* vinyl oxiranes can be stereoselectively ring expanded to *cis*- and *trans*-2,5-dihydrofuran products respectively.[3] Not surprisingly, and in accordance with our oxirane-olefin chelation model, the corresponding *Z*-olefins were shown to be poor substrates with the exception being cyclic vinyl oxiranes.



Scheme 5.9: Chelation Model for Stereoselective Oxirane Ring Expansion

In this chelation scheme, we envision initial coordination of the copper catalyst to the lone pairs of the oxirane atom followed by coordination to the olefin prior to ring expansion. The 2,5-dihydrofuran (**5.44**) product forms a less effective chelate with the catalyst and is therefore quickly released to turnover the catalyst. The main competing pathway for this ring expansion is highly dependent on the steric and electronic nature of the vinyl oxirane being investigated. If ring expansion does not occur rapidly, an allylic cation (**5.48**) can be formed that can either form the isomeric oxirane and then ring expand or alternatively undergo a 1,2-hydride shift to form **5.49**.

In conclusion, we have explored the suitability of our new copper catalyzed vinyl oxirane ring expansion reaction for the total synthesis of varitriol. In our opinion, this reaction is a good match for varitriol as is evident from our expedient approaches. To realize this goal, the important secondary challenge of this project became to design an optimal synthesis of the vinyl oxirane precursor and the most efficient sequence from the dihydrofuran product. This reminds us that in order to accomplish short and efficient syntheses, a good method needs the support of good synthetic design and insightful selection of starting materials. The message of these synthetic explorations towards varitriol is clear. New synthetic methods provide new opportunities for synthetic design, which in turn enable better approaches to well matched targets. This means that there is a great need for developing useful new synthetic methods, especially asymmetric ones that can complement the use of chiral pool source materials.

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APPENDIX 1

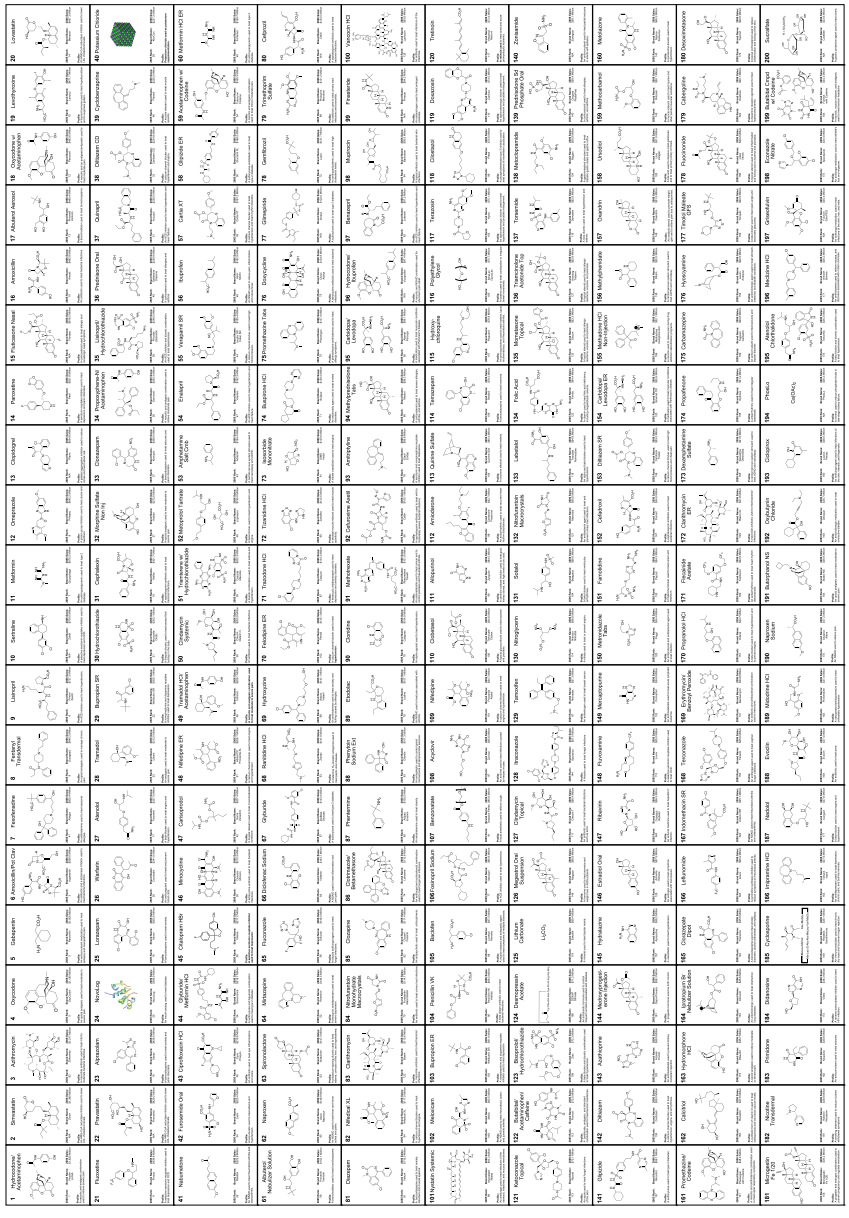


Figure A1.1: Top 200 Generic Drugs by Retail Dollars in 2006

Top 200 Brand-Name Drugs by Retail Dollars in 2006

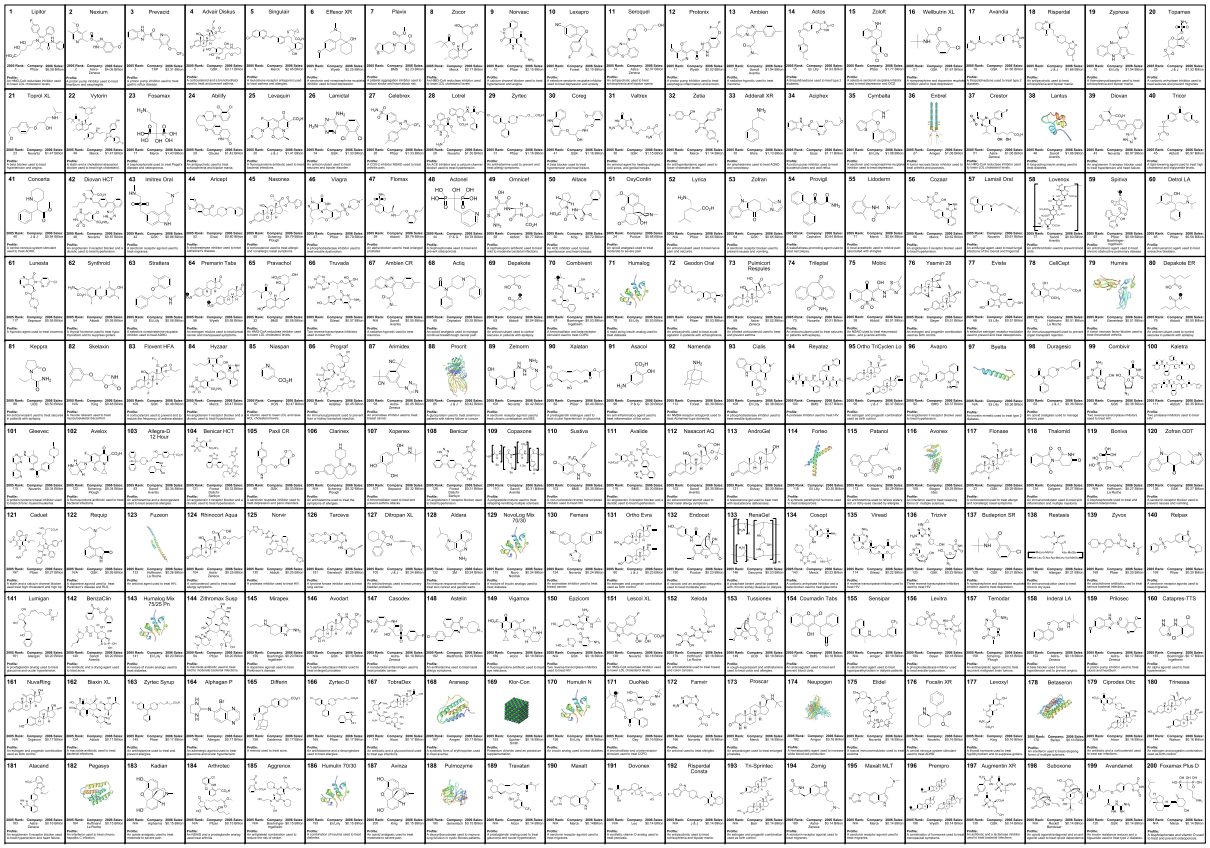
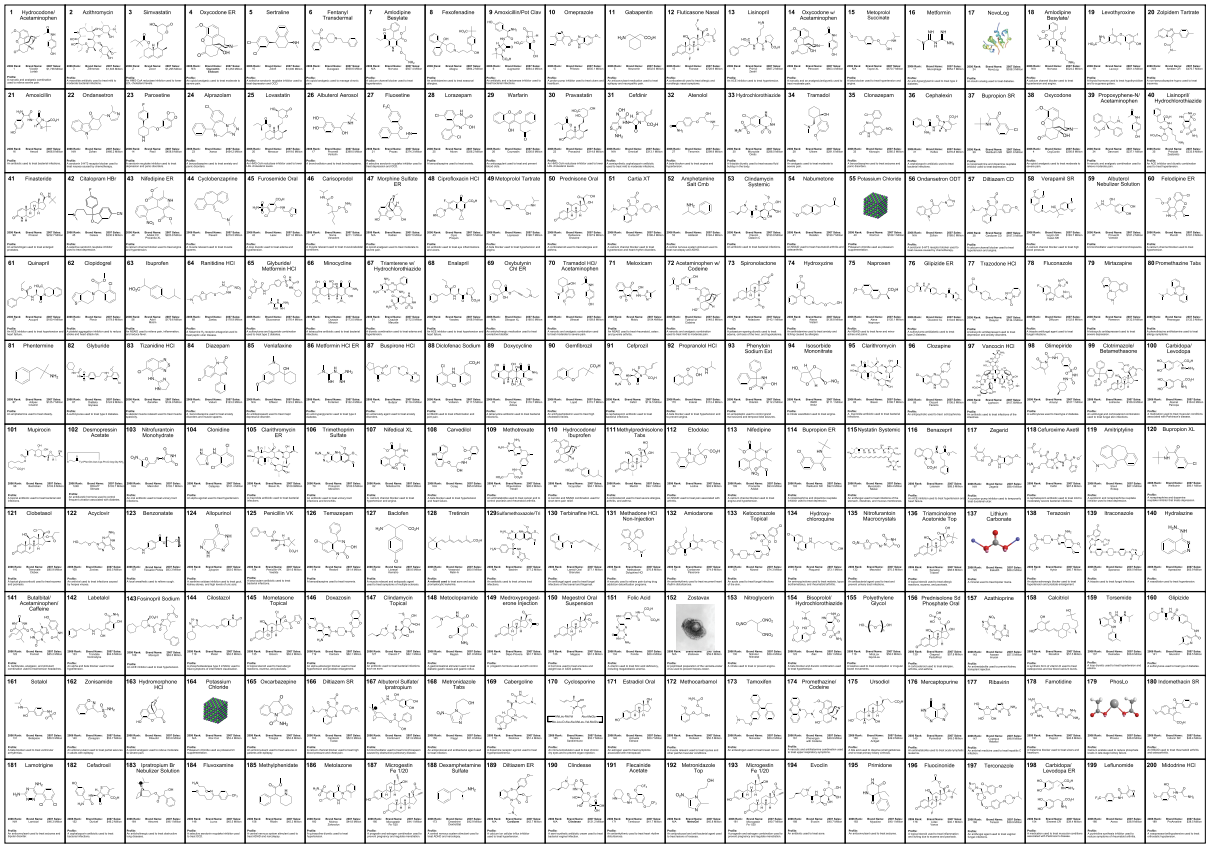


Figure A1.2: Top 200 Brand-Name Drugs by Retail Dollars in 2006

Top 200 Generic Drugs by Retail Dollars in 2007



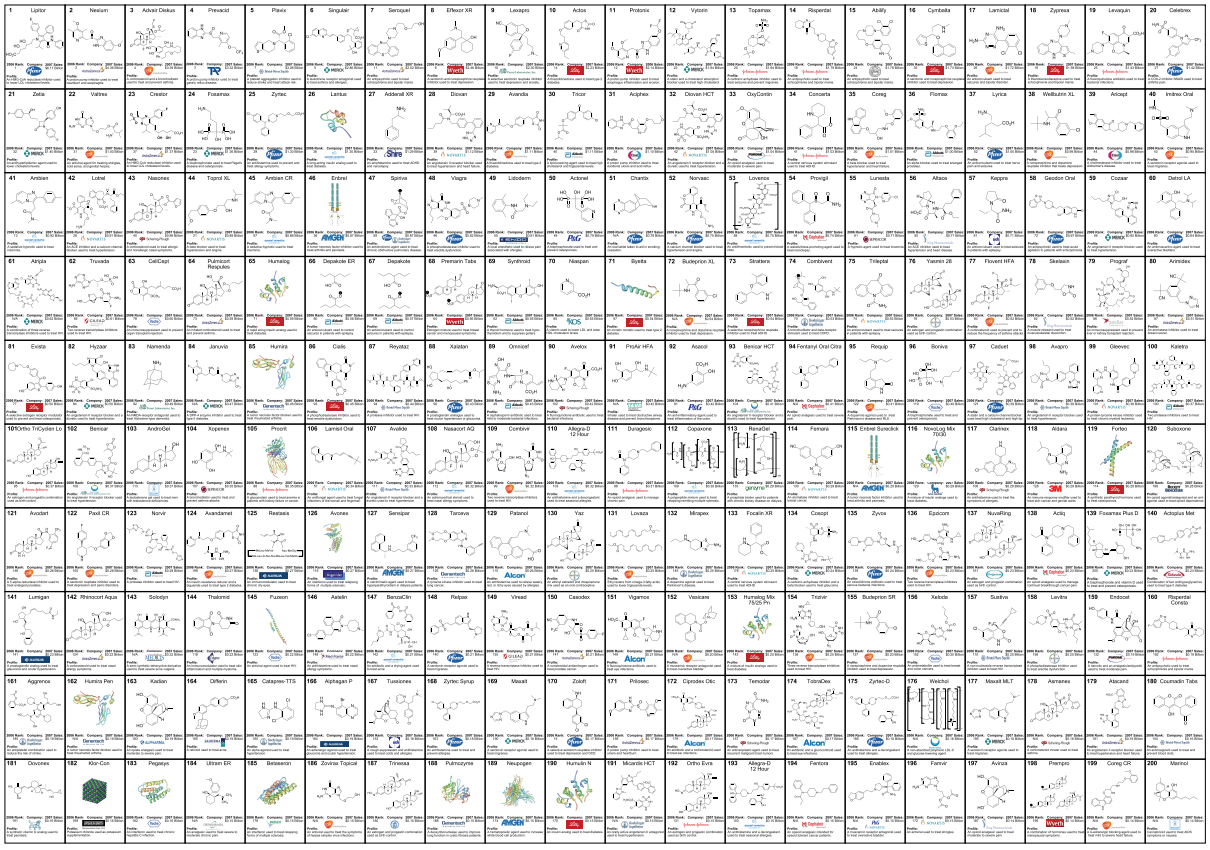
Reference
http://drugtopics.modernmedicine.com/drugtopics/data/articlestandard/drugtopics/872008/391181/article.pdf

Compiled and Produced by the Njardarson Group:
Eric Brooks, Nicholas McGrath, Matthew Brichacek,
Jason Morton, Lindsay Batory, Laura Kwon, Jón T. Njarðarson

Cornell University

Figure A1.3: Top 200 Generic Drugs by Retail Dollars in 2007

Top 200 Brand-Name Drugs by Retail Dollars in 2007



Compiled and Produced by the Njardarson Group:
Eric Brooks, Matthew Brichacek, Nicholas McGrath,
Jason Morton, Lindsay Batory, Jón T. Njarðarson

Cornell University

Figure A1.4: Top 200 Brand-Name Drugs by Retail Dollars in 2007

Top 200 Generic Drugs by Retail Dollars in 2008

Figure A1.5: Top 200 Generic Drugs by Retail Dollars in 2008

Top 200 Brand-Name Drugs by Retail Dollars in 2008

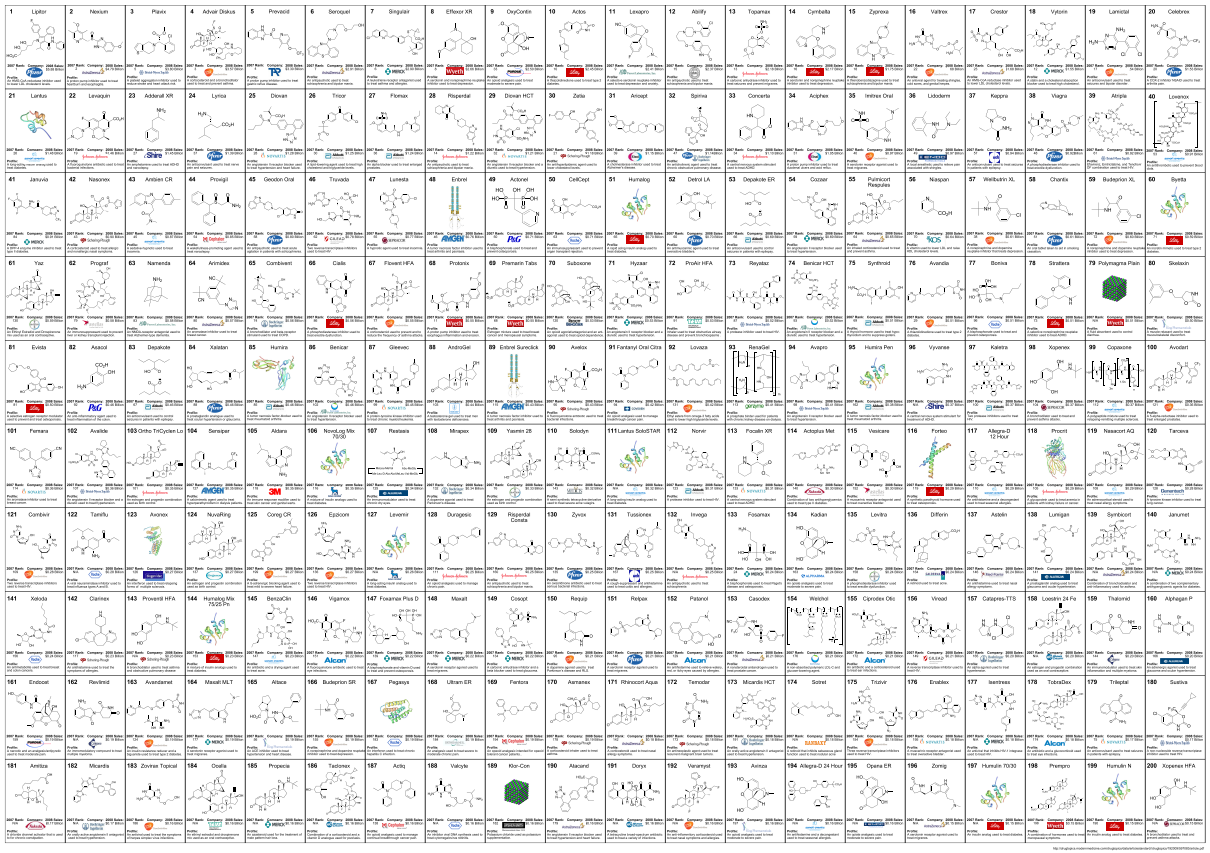


Figure A1.6: Top 200 Brand-Name Drugs by Retail Dollars in 2008

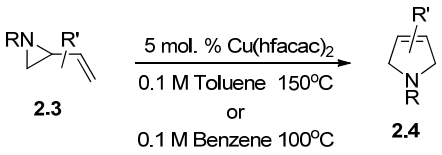
APPENDIX 2

A2.1 Experimental Procedures for Chapter 2

General Information:

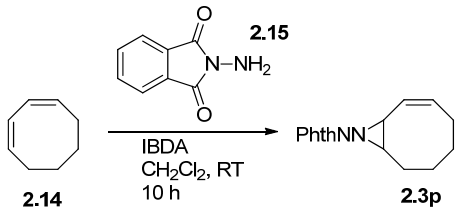
Commercial reagents were purchased and used without further purification. All glassware was flame- or oven-dried prior to use and reactions were performed under a nitrogen atmosphere unless otherwise noted. Toluene, benzene, dichloromethane, diethyl ether, and THF were dried over a column of alumina. Flash chromatography was preformed using MP Silitech 32-63D 60Å silica. Thin layer chromatography (TLC) was done with EMD 250 μm silica gel 60-F254 plates. ^{1}H and ^{13}C NMR data were acquired on a Varian Mercury 300 (300 MHz) or a Varian Inova 400, 500, or 600 (400, 500 or 600 MHz) spectrometer and referenced to residual protic solvent or TMS as an internal standard. IR spectroscopy was done on a Mattson RS-10500 FTIR spectrometer. High-resolution mass spectrometry was performed at the University of Illinois at Urbana-Champaign facility.

General Procedure for the Rearrangement of Vinylaziridines to 3-Pyrrolines (Procedure A):



To a 4 mL disposable Fisherbrand® vial was added $Cu(hfacac)_2 \bullet H_2O$ (0.005 mmol, 5 mol %) and dried[1] by placing under a vacuum until color change was observed (1-3 h). To the catalyst was added a solution of the vinyl aziridine (0.10 mmol) in toluene/benzene (0.1 M). The vial was sealed with a Teflon® cap and heated at 100 °C or 150 °C until the reaction was complete (TLC or NMR). After cooling to room temperature the reaction mixture was filtered through neutral alumina (activity grade 1) washing with CH_2Cl_2 or EtOAc. The solvent was removed *in vacuo* often resulting in a product that required no further purification. When purification was necessary, flash chromatography with silica was preformed.

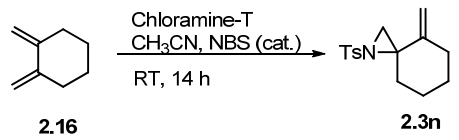
Representative Procedure for the Preparation of Phthalimide Aziridines (Procedure B):



N-Phthalimido-9-aza-bicyclo [6.1.0] non-2-ene (**2.3p**): Cis,cis-1,3-cyclooctadiene (0.10 g, 0.92 mmol, 1 equiv) was dissolved in dry CH_2Cl_2 (9.2 mL, 0.1 M) and N-amino-phthalimide (0.187 g, 1.15 mmol, 1.25 equiv.) was added. The heterogeneous solution was stirred vigorously while iodobenzenediacetate (0.326 g, 1.01 mmol, 1.1 equiv.) was added portion wise over 1 hour. The solution was stirred at room temperature for 14 hours. The reaction was diluted with CH_2Cl_2, washed with sat. $NaHCO_3$, and dried over Na_2SO_4. The solvent was evaporated and crude mixture purified by flash chromatography (R_f = 0.5, 1:1 ether:pentane). Yield 131 mg (53%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.77 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.67 (dd, *J* = 5.4, 3.0 Hz, 2H), 5.94 (dd, *J* = 11.2, 1.2 Hz, 1H), 5.84 (dddd, *J* = 11.2, 7.4, 5.4, 1.9 Hz, 1H), 3.11-3.06 (m, 1H), 2.84-2.78 (m, 1H), 2.48-2.39 (m, 1H), 2.33 (dddd, *J* = 16.2, 10.0, 7.4, 1.4 Hz, 1H), 2.06-1.96 (m, 1H), 1.85-1.73 (m, 1H), 1.73-1.64 (m, 2H), 1.63-1.54 (m, 1H), 1.52-1.43 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$ δ ppm 165.1, 135.1, 133.9, 130.6, 122.9, 122.2, 50.7, 46.7, 28.8, 26.2, 26.1, 25.6. **IR** (neat) 2927, 2866, 1712, 1378, 1184, 1153, 1048, 913, 745, 709, 526 cm^{-1}. **ESMS** m/z 291.1 ($[M+Na]^+$); **HRESMS** m/z calcd for $C_{16}H_{16}N_2O_2Na$ ($[M+Na]^+$) 291.1109 found 291.1129.

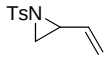
Representative Procedure for the Preparation of Tosyl Aziridines (Procedure C):



2,2-Spiromethylenecyclohexane-N-(p-Toluenesulfonyl)-aziridine (**2.3n**): To a 100 mL flame-dried round bottom flask was added 30 mL of dry CH_3CN. Then 1,2-dimethylenecyclohexane[2] (700 mg, 6.5 mmol, 1.0 equiv) and anhydrous chloramine-T[25] (1.47 g, 6.5 mmol, 1.0 equiv) were added. To this solution N-bromosuccinimide (0.23 g, 1.3 mmol, 0.2 equiv.) was added slowly over 30 min. The solution was stirred 14 hours and then diluted with EtOAc and washed with sat. aqueous $NaHCO_3$ and dried over Na_2SO_4. The solvent was evaporated and the crude mixture was purified by flash chromatography (R_f = 0.51, 30% EtOAc:70% hexanes). Yield 120 mg (7%).

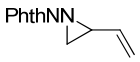
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.85 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 4.95 (s, 1H), 4.78 (s, 1H), 2.65 (s, 1H), 2.52-2.44 (m, 1H), 2.43 (s, 3H), 2.39 (s, 1H),

2.26-2.03 (m, 3H), 2.03-1.93 (m, 1H), 1.76-1.55 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$ δ ppm 145.7, 143.8, 137.8, 129.4, 127.4, 109.1, 55.5, 41.0, 34.5, 32.8, 27.1, 25.6, 21.6. **IR** (neat) 2936, 2859, 1598, 1322, 1160, 816, 714, 567 cm^{-1}. **ESMS** m/z 278.1 ($[M+H]^+$); **HRESMS** m/z calcd for $C_{15}H_{20}NO_2S$ ($[M+H]^+$) 278.1215 found 278.1222.



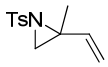
1-Tosyl-2-vinylaziridine (**2.3a**): Prepared according to general procedure C. Spectra matched existing literature data.[3]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 – 7.80 (m, 2H), 7.35 – 7.31 (m, 2H), 5.56 – 5.45 (m, 1H), 5.45 – 5.37 (m, 1H), 5.26 – 5.20 (m, 1H), 3.31 – 3.21 (m, 1H), 2.77 (dd, *J* = 7.1, 1.7, 1H), 2.47 – 2.39 (m, 3H), 2.21 (dd, *J* = 4.5, 1.1, 1H).



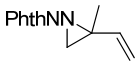
N-Phthalimido-2-vinylaziridine (**2.3b**): Prepared according to general procedure B. Spectra matched existing literature data.[4]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 – 7.77 (m, 2H), 7.70 – 7.68 (m, 2H), 5.77 (ddd, *J* = 17.4, 10.4, 7.2, 1H), 5.56 (ddd, *J* = 17.2, 1.3, 0.8, 1H), 5.37 (ddd, *J* = 10.4, 1.3, 0.6, 1H), 3.09 (ddd, *J* = 13.0, 7.2, 5.8, 1H), 2.73 (dd, *J* = 7.8, 2.4, 1H), 2.53 (dd, *J* = 5.8, 2.4, 1H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 164.8, 134.2, 134.0, 130.1, 122.9, 119.4, 43.9, 38.6.



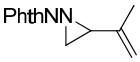
2-Methyl-N-(p-Toluenesulfonyl)-2-vinylaziridine (**2.3c**): Prepared according to general procedure C.[5]

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 1.65 (s, 3H), 2.42 (s, 3H), 2.61 (s, 1H), 2.63 (s, 1H), 5.31 (d, *J* = 10.7 Hz, 1H), 5.41 (d, *J* = 17.2 Hz, 1H), 5.97 (dd, *J* = 17.2, 10.7 Hz, 1H), 7.31 (d, *J* = 8.2 Hz, 2H) 7.82 (d, *J* = 8.2 Hz, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 143.9, 137.5, 136.9, 129.5, 127.3, 118.3, 49.8, 42.0, 21.6, 18.5; **IR** (neat) 2989, 2927, 1598, 1321, 1161, 817, 732, 568 cm^{-1}; **ESMS** m/z 238.1 ($[M+H]^+$); **HRESMS** m/z calcd for $C_{12}H_{16}NO_2S$ ($[M+H]^+$) 238.0902 found 238.0896.



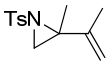
N-Phthalimido-(2-methyl-2-vinylaziridine) (**2.3d**): Prepared according to general procedure B. Spectra matched existing literature data.[6]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 (dd, *J* = 5.6, 3.0, 2H), 7.73 (dd, *J* = 5.4, 3.2, 2H), 6.09 (dd, *J* = 17.6, 11.0, 1H), 5.28 (d, *J* = 17.6, 1H), 5.21 (d, *J* = 11.0, 1H), 3.36 (d, *J* = 12.4, 1H), 3.29 (d, *J* = 12.4, 1H), 1.98 (s, 3H).



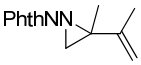
N-Phthalimido-2-(prop-1-en-2-yl)aziridine (**2.3e**): Prepared according to general procedure B. Spectra matched existing literature data.[7]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 – 7.76 (m, 2H), 7.69 – 7.67 (m, 2H), 5.17 (dt, *J* = 1.7, 0.9, 1H), 5.09 (t, *J* = 1.5, 1H), 3.06 (t, *J* = 6.9, 1H), 2.69 – 2.57 (m, 1H), 1.86 (s, 3H).



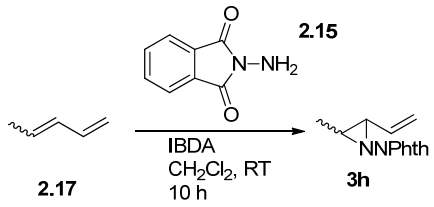
2-Methyl-N-(p-toluenesulfonyl)-2-isopropenylaziridine (**2.3f**): Prepared according to general procedure C. [8]

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.83 (d, *J* = 8.3 Hz, 2H), 7.31 (d, *J* = 8.3 Hz, 2H), 4.99 (d, *J* = 0.6 Hz, 1H), 4.89 (d, J = 0.6 Hz, 1H), 2.75 (s, 1H), 2.42 (s, 3H), 2.42 (s, 1H), 1.82 (s, 3H), 1.78 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 144.4, 143.8, 137.8, 129.5, 127.4, 113.2, 53.2, 41.0, 21.6, 19.0, 18.0. **IR** (neat) 2978, 1598, 1450, 1322, 1159, 873, 817, 712, 570 cm^{-1}. **ESMS** m/z 252.1 ($[M+H]^+$); **HRESMS** m/z calcd for $C_{13}H_{18}NO_2S$ ($[M+H]^+$) 252.1058 found 252.1059.



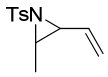
N-Phthalimido--(2-methyl-2-(prop-1-en-2-yl)aziridine (**2.3g**): Prepared according to general procedure B. Spectra matched existing literature data.[9]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 – 7.74 (m, 1H), 7.71 – 7.67 (m, 1H), 5.13 (s, 0H), 5.00 (d, *J* = 1.4, 1H), 2.89 (d, *J* = 2.5, 0H), 2.75 (s, 1H), 1.99 (s, 1H), 1.42 (s, 1H).



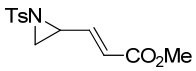
3-Methyl-N-(phthalimido)-2-vinylaziridine (**2.3h**, trans:cis 2.5:1): Piperylene (technical grade, 0.10 g, 1.47 mmol, 1 equiv) was dissolved in dry CH_2Cl_2 (7.3 mL, 0.1 M) and N-amino-phthalimide (0.298 g, 1.84 mmol, 1.25 equiv.) was added. The heterogeneous solution was stirred vigorously while iodobenzenediacetate (0.521 g, 1.62 mmol, 1.1 equiv.) was added portion wise over 1 hour. The solution was stirred at room temperature for 6 hours. The reaction was diluted with CH_2Cl_2, washed with sat. $NaHCO_3$, and dried over Na_2SO_4. The solvent was evaporated and crude mixture purified by flash chromatography (R_f = 0.4, 50% ether:50% pentane). Yield 101 mg (30%).

trans: **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.75 (dd, *J* = 5.6, 3.0 Hz, 2H), 7.67 (dd, *J* = 5.6, 3.0 Hz, 2H), 5.62 (ddd, *J* = 17.1, 10.3, 7.9 Hz, 1H), 5.41 (ddd, *J* = 17.1, 1.3, 0.6 Hz, 1H), 5.27-5.23 (m, 1H), 3.28-3.17 (m, 1H), 2.93 (dq, *J* = 7.9, 5.6 Hz, 1H), 1.48 (d, *J* = 5.6 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 165.8, 134.6, 134.0, 131.0, 122.9, 121.4, 50.9, 43.2, 17.0.
cis: **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.78 (dd, *J* = 5.6, 2.9 Hz, 2H), 7.69 (dd, *J* = 5.6, 2.9 Hz, 2H), 5.77 (ddd, *J* = 17.4, 10.4, 7.2 Hz, 1H), 5.54 (ddd, *J* = 17.4, 1.5, 0.7 Hz, 1H), 5.33 (ddd, *J* = 10.4, 1.5, 0.7 Hz, 1H), 3.26-3.18 (m, 1H), 2.67 (td, *J* = 5.9, 5.9 Hz, 1H), 1.36 (d, *J* = 5.9 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 166.2, 134.3, 133.9, 130.4, 123.0, 119.0, 48.8, 45.1, 12.9.
IR (neat) 2975, 2931, 1881, 1717, 1612, 1466, 1375, 1187, 1134, 984, 896, 709, 526 cm^{-1}. **ESMS** m/z 229.1 ($[M+H]^+$); **HRESMS** m/z calcd for $C_{13}H_{13}N_2O_2$ ($[M+H]^+$) 229.0977 found 229.0972.



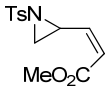
2-Methyl-1-tosyl-3-vinylaziridine (**2.3i**): Prepared according to existing literature procedure and spectra matched existing literature data.[10]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.3, 2H), 7.31 (d, *J* = 0.6, 2H), 5.59 (ddd, *J* = 17.3, 10.4, 7.0, 1H), 5.39 (ddd, *J* = 17.2, 1.5, 0.9, 1H), 5.29 (ddd, *J* = 10.4, 1.4, 0.7, 1H), 3.32 (dd, *J* = 12.4, 5.2, 1H), 3.02 (dq, *J* = 7.3, 5.8, 1H), 2.43 (s, 3H), 1.19 (d, *J* = 5.8, 3H).



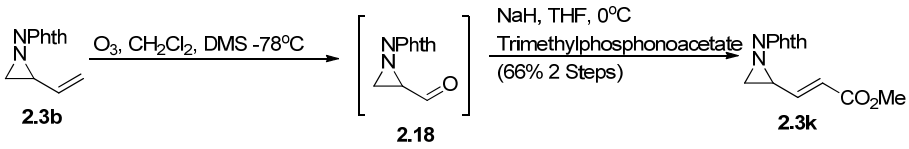
(E)-Methyl 3-(1-tosylaziridin-2-yl)acrylate (**2.3j**): Prepared according to existing literature procedure and spectra matched existing literature data.[11]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.3, 2H), 7.34 (dd, *J* = 8.6, 0.6, 2H), 6.55 (dd, *J* = 15.6, 7.5, 1H), 6.10 (dd, *J* = 15.6, 0.7, 1H), 3.71 (s, 3H), 3.37 – 3.29 (m, 1H), 2.87 (d, *J* = 7.1, 1H), 2.44 (s, 3H), 2.26 (d, *J* = 4.2, 1H).



(Z)-Methyl 3-(1-tosylaziridin-2-yl)acrylate (**2.3j cis**): Prepared according to existing literature procedure and spectra matched existing literature data.[12]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.3, 2H), 7.34 (d, *J* = 8.0, 2H), 5.95 (d, *J* = 11.5, 1H), 5.68 (dd, *J* = 11.5, 8.9, 1H), 4.54 – 4.44 (m, 1H), 3.76 (s, 3H), 2.92 (d, *J* = 7.3, 1H), 2.44 (s, 3H), 2.26 (d, *J* = 4.3, 1H).

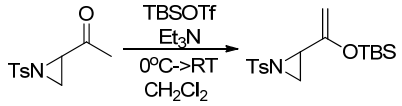


N-Phthalimido-2-propenoic acid methyl ester-aziridine (**2.3k**): **2.3b** (25.0 mg, 1.17 mmol, 1 equiv.) was dissolved in CH_2Cl_2 (1.2 mL, 0.1 M) and cooled to -78 °C under an atmosphere of nitrogen. Ozone was bubbled through the solution and the reaction was monitored by TLC (~3 hours). The solution was flushed with nitrogen and quenched with dimethyl sulfide (0.035 mL, 4.67 mmol, 4 equiv). The reaction was warmed to room temperature and the solvent removed. The product (**2.18**) is unstable at room temperature and was used without purification.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 9.27 (d, *J* = 5.2 Hz, 1H), 7.93-7.67 (m, 4H), 3.23 (ddd, *J* = 8.2, 5.2, 5.2 Hz, 1H), 3.03 (dd, *J* = 8.2, 2.1 Hz, 1H), 2.88 (dd, *J* = 5.2, 2.1 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 196.2, 164.5, 134.5, 129.9, 123.4, 45.9, 34.8. **IR** (neat) 2935, 1786, 1723, 1468, 1380, 913, 743, 712 cm^{-1}.

In a flame-dried flask under nitrogen, NaH (5.5 mg, 2 equiv) was dissolved in 1 mL of THF and cooled to 0 °C. Trimethylphosphonoacetate (0.047 mL, 2 equiv) was added drop wise to the solution and allowed to stir for 30 minutes. Then, the crude aldehyde prepared before (~25 mg) was dissolved in 0.5 mL of anhydrous THF and added slowly. The solution was stirred at 0 °C and monitored by TLC (~4h). The reaction was quenched with 1 mL of distilled H_2O, then extracted with CH_2Cl_2, dried on Na_2SO_4, and the solvent removed. (crude E:Z 17:1). The product can be purified by silica gel chromatorgraphy (50% ether:50% pentane, R_f = 0.36) yield 21.0 mg (66%).

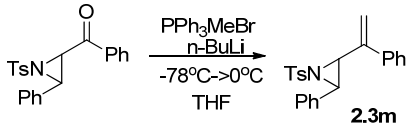
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.79 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.70 (dd, *J* = 5.4, 3.1 Hz, 2H), 6.79 (dd, *J* = 15.7, 7.5 Hz, 1H), 6.26 (dd, *J* = 15.7, 0.8 Hz, 1H), 3.76 (s, 3H), 3.21-3.13 (m, 1H), 2.87 (dd, *J* = 7.9, 2.2 Hz, 1H), 2.57 (dd, *J* = 5.5, 2.2 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 166.2, 164.8, 143.6, 134.2, 130.1, 124.2, 123.2, 51.7, 42.1, 39.4. **IR** (neat) 2921, 2852, 1716, 1437, 1376, 1274, 1201, 1045, 977, 913, 745 cm^{-1}. **ESMS** m/z 293.0 ([M-H_2+Na]$^+$); **HRESMS** m/z calcd for $C_{14}H_{10}N_2O_4Na$ ([M-H_2+Na]$^+$) found 293.0546.



2.19 **2.3l**

2-(1-(t-Butyldimethylsilyloxy)vinyl)-N-tosylaziridine (**2.3l**): 1-(*N*-Tosylaziridin-2-yl)ethanone[13] (1.1 g, 4.6 mmol, 1 equiv) was dissolved in 23 mL of CH_2Cl_2 (0.2 M) and cooled to 0 °C. Et_3N (3.8 mL, 27.6 mmol, 6 equiv.) was added followed by addition of TBSOTf (2.3 mL, 10.1 mmol, 2.2 equiv.) drop wise. The reaction was warmed to room temperature. After 2 h the reaction was quenched with sat. NaCl and extracted with CH_2Cl_2. The solution was dried with Na_2SO_4 and the solvent removed *in vacuo* . The product was purified using flash chromatography (R_f = 0.45, 30% EtOAc:70% hexanes). Yield = 1.50 g (96%,).

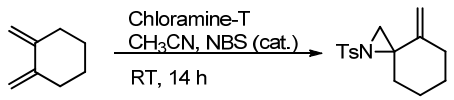
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.81 (d, *J* = 8.0 Hz, 2H), 7.33 (d, *J* = 8.0 Hz, 2H), 4.44 (s, 1H), 4.28 (s, 1H), 3.21 (dd, *J* = 6.9, 4.4 Hz, 1H), 2.64 (d, *J* = 6.9 Hz, 1H), 2.44 (s, 3H), 2.40 (d, J = 4.4 Hz, 1H), 0.85 (s, 9H), 0.08 (s, 3H), 0.05 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 151.4, 144.3, 135.0, 129.5, 127.7, 95.2, 41.0, 31.1, 25.4, 21.5, 18.0, -4.8, -5.3. **IR** (neat) 2955, 2930, 2858, 1639, 1463, 1330, 1254, 1162, 1029, 940, 840, 682, 560 cm^{-1}. **ESMS** m/z 354.1 ([M+H]$^+$); **HRESMS** m/z calcd for $C_{17}H_{28}NO_3SiS$ ([M+H]$^+$) 354.1559 found 354.1561.



2.20 **2.3m**

2-Phenyl-3-(1-phenylvinyl)-N-tosylaziridine (**2.3m**): PPh_3MeBr (10.3 mg, 0.029 mmol, 1.5 equiv.) was added to 0.25 ml of THF at -78 °C. To this solution n-BuLi (1.6 M in hexanes, 0.018 ml, 0.029 mmol, 1.5 equiv.) was added and warmed to 0 °C while stirring for 30 min. A solution of Phenyl(3-phenyl-*N*-Tosylaziridine-2-yl)methanone[14] (7.0 mg, 0.19 mmol, 1 equiv.) in 0.25 ml of THF was added. The reaction was warmed to room temperature and stirred for 1 hour. The solution was diluted with ether, washed with sat NH_4Cl, and dried with Na_2SO_4. The solvent was removed *in vacuo* and purified using flash chromatography (R_f = 0.45, 30% EtOAc:70% hexanes). Yield = 5.0 mg, (72%).

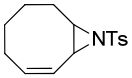
^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.62 (d, *J* = 8.2 Hz, 2H), 7.47-7.36 (m, 4H), 7.33 (bs, 3H), 7.32-7.25 (m, 3H), 7.16 (d, *J* = 8.2 Hz, 2H), 5.58 (bs, 1H), 5.41 (bs, 1H), 4.18 (d, *J* = 4.7 Hz, 1H), 3.97 (d, *J* = 4.7 Hz, 1H), 2.35 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 143.9, 141.0, 138.2, 136.9, 132.0, 129.3, 128.8, 128.4, 128.4, 128.2, 128.1, 127.5, 126.1, 115.8, 51.0, 48.8, 21.5. **IR** (neat) 3060, 3031, 2923, 1598, 1496, 1328, 1162, 1087, 931, 911, 752, 697 cm^{-1}. **ESMS** m/z 398.1($[M+Na]^+$); **HRESMS** m/z calcd for $C_{23}H_{21}NO_2NaS$ ($[M+Na]^+$) 398.1191 found 398.1182.



2.16 **2.3n**

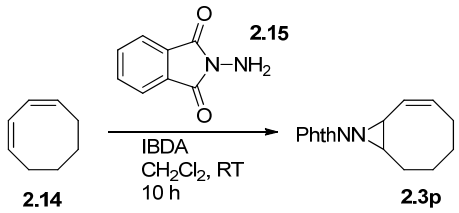
2,2-Spiromethylenecyclohexane-N-(p-toluenesulfonyl)-aziridine (**2.3n**): In a 100 mL flame-dried round bottom flask was added 30 mL of dry CH_3CN. To this solution was added 1,2-dimethylenecyclohexane[15] (700 mg, 6.5 mmol, 1.0 equiv) and anhydrous chloramine-T[25] (1.47 g, 6.5 mmol, 1.0 equiv). To this solution N-bromosuccinimide (0.23 g, 1.3 mmol, 0.2 equiv.) was added slowly over 30 min. The solution was stirred 14 hours and then diluted with EtOAc and washed with sat. aqueous $NaHCO_3$ and dried over Na_2SO_4. The solvent was evaporated and the crude mixture was purified by flash chromatography (R_f = 0.51, 30% EtOAc:70% hexanes). Yield 120 mg (7%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.85 (d, *J* = 8.1 Hz, 2H), 7.31 (d, *J* = 8.1 Hz, 2H), 4.95 (s, 1H), 4.78 (s, 1H), 2.65 (s, 1H), 2.52-2.44 (m, 1H), 2.43 (s, 3H), 2.39 (s, 1H), 2.26-2.03 (m, 3H), 2.03-1.93 (m, 1H), 1.76-1.55 (m, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 145.7, 143.8, 137.8, 129.4, 127.4, 109.1, 55.5, 41.0, 34.5, 32.8, 27.1, 25.6, 21.6. **IR** (neat) 2936, 2859, 1598, 1322, 1160, 816, 714, 567 cm^{-1}. **ESMS** m/z 278.1 ($[M+H]^+$); **HRESMS** m/z calcd for $C_{15}H_{20}NO_2S$ ($[M+H]^+$) 278.1215 found 278.1222.



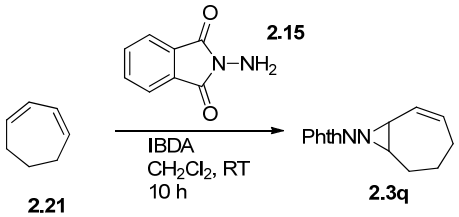
N-Tosyl-9-aza-bicyclo[6.1.0]non-2-ene (**2.3o**): Prepared according to general procedure B.[16]

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.79 (d, *J* = 8.21 Hz, 2H), 7.29 (d, *J* = *8.2* Hz, 2H), 5.71 (dddd, *J* = 11.1, 7.5, 5.7, 1.8 Hz, 1H), 5.29 (dd, *J* = 11.1, 1.1 Hz, 1H), 3.36-3.30 (m, 1H), 2.94 (ddd, *J* = 10.3, 7.0, 3.6 Hz, 1H), 2.40 (s, 3H), 2.30-2.14 (m, 1H), 2.05-1.86 (m, 2H), 1.83-1.46 (m, 3H), 1.44-1.26 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 144.2, 135.6, 135.5, 129.6, 127.6, 120.5, 46.1, 42.4, 28.7, 26.1, 26.0, 25.3, 21.6. **IR** (neat) 3031, 2930, 2866, 1598, 1322, 1159, 1092, 952, 662, 573 cm^{-1}. **ESMS** m/z 278.1 ($[M+H]^+$); **HRESMS** m/z calcd for $C_{15}H_{20}NO_2S$ ($[M+H]^+$) 278.1215 found 278.1222.



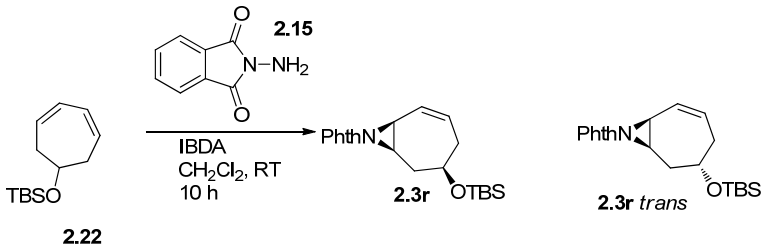
N-Phthalimido-9-aza-bicyclo [6.1.0] non-2-ene (**2.3p**): Cis,cis-1,3-cyclooctadiene (0.10 g, 0.92 mmol, 1 equiv) was dissolved in dry CH_2Cl_2 (9.2 mL, 0.1 M) and N-amino-phthalimide (0.187 g, 1.15 mmol, 1.25 equiv.) was added. The heterogeneous solution was stirred vigorously while iodobenzenediacetate (0.326 g, 1.01 mmol, 1.1 equiv.) was added portion wise over 1 hour. The solution was stirred at room temperature for 14 hours. The reaction was diluted with CH_2Cl_2, washed with sat. $NaHCO_3$, and dried over Na_2SO_4. The solvent was evaporated and crude mixture purified by flash chromatography (R_f = 0.5, 50% ether:50% pentane). Yield 131 mg (53%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.77 (dd, *J* = 5.4, 3.0 Hz, 2H), 7.67 (dd, *J* = 5.4, 3.0 Hz, 2H), 5.94 (dd, *J* = 11.2, 1.2 Hz, 1H), 5.84 (dddd, *J* = 11.2, 7.4, 5.4, 1.9 Hz, 1H), 3.11-3.06 (m, 1H), 2.84-2.78 (m, 1H), 2.48-2.39 (m, 1H), 2.33 (dddd, *J* = 16.2, 10.0, 7.4, 1.4 Hz, 1H), 2.06-1.96 (m, 1H), 1.85-1.73 (m, 1H), 1.73-1.64 (m, 2H), 1.63-1.54 (m, 1H), 1.52-1.43 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 165.1, 135.1, 133.9, 130.6, 122.9, 122.2, 50.7, 46.7, 28.8, 26.2, 26.1, 25.6. **IR** (neat) 2927, 2866, 1712, 1378, 1184, 1153, 1048, 913, 745, 709, 526 cm^{-1}. **ESMS** m/z 291.1 ($[M+Na]^+$); **HRESMS** m/z calcd for $C_{16}H_{16}N_2O_2Na$ ($[M+Na]^+$) 291.1109 found 291.1129.



N-Phthalimido-8-aza-bicyclo [5.1.0] oct-2-ene (**2.3q**): Cis,cis-1,3-cyclooheptadiene (0.10 g, 1.06 mmol, 1 equiv) was dissolved in dry CH_2Cl_2 (10.6 mL, 0.1 M) and N-amino-phthalimide (0.215 g, 1.33 mmol, 1.25 equiv.) was added. The heterogeneous solution was stirred vigorously while iodobenzenediacetate (0.376 g, 1.17 mmol, 1.1 equiv.) was added portion wise over 1 hour. The solution was stirred at room temperature for 14 hours. The reaction was diluted with CH_2Cl_2, washed with sat. $NaHCO_3$, and dried over Na_2SO_4. The solvent was evaporated and crude mixture purified by flash chromatography (R_f = 0.4, 30% ether:70% pentane). Yield 270 mg (71%).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.76 (2 H, dd, J = 5.4, 3.0 Hz), 7.67 (2 H, dd, J = 5.4, 3.0 Hz), 6.14 (1 H, m), 5.93 (1 H, m), 3.06 (1 H, ddd, J = 8.2, 4.1, 4.1 Hz), 2.89 (1 H, ddd, J = 8.2, 5.1, 0.57 Hz), 2.58-2.52 (1 H, m), 2.33-2.25 (1 H, m), 2.12-2.01 (2 H, m), 1.70-1.63 (2 H, m). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 165.1, 137.1, 133.9, 130.5, 123.3, 122.9, 52.1, 47.8, 31.1, 29.0, 23.7. **IR** (neat) 3020, 2930, 1713, 1377, 1156, 909, 987, 707 cm^{-1}; **ESMS** m/z 255.1 ($[M+H]^+$); **HRESMS** m/z calcd for $C_{15}H_{15}N_2O_2$ ($[M+H]^+$) 255.1134 found 255.1127.

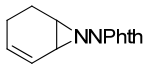


5-(tert-Butyldimethylsilyloxy)-N-phthalimido-8-aza-bicyclo [5.1.0] oct-2-ene (**2.3r** *cis*): tert-Butyl((3Z,5Z)-cyclohepta-3,5-dienyloxy)dimethylsilane[17] (0.10 g, 0.45 mmol, 1 equiv) was dissolved in dry CH_2Cl_2 (4.5 mL, 0.1 M) and N-amino-phthalimide (0.091 mg, 0.56 mmol, 1.25 equiv.) was added. The heterogeneous solution was stirred vigorously while iodobenzenediacetate (0.159 g, 0.50 mmol, 1.1 equiv.) was added portion wise over 1 hour. The solution was stirred at room temperature for 20 hours. The reaction was diluted with CH_2Cl_2, washed with sat. $NaHCO_3$, and dried over Na_2SO_4. The solvent was evaporated and crude mixture purified by flash chromatography (R_f = 0.5, 20% ether:80% pentane). Yield 81 mg (47%).

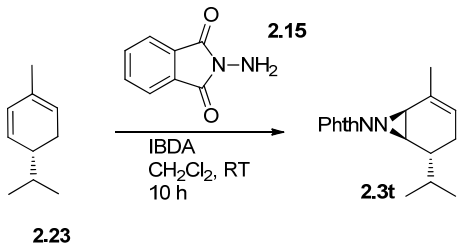
(**2.3r** *cis*): **^{1}H NMR** (600 MHz, $CDCl_3$) δ 7.77 (dd, J = 5.5, 3.0 Hz, 2H), 7.68 (dd, J = 5.5, 3.0 Hz, 2H), 6.13 (dddd, J = 11.3, 3.1, 2.0, 1.2 Hz, 1H), 5.68-5.64 (m, 1H), 3.98 (dddd, J = 10.8, 8.3, 4.5, 2.3 Hz, 1H), 2.94 (dt, J = 8.2, 8.1, 0.6 Hz, 1H), 2.90 (dd, J = 7.8, 1.6 Hz, 1H), 2.77-2.72 (m, 1H), 2.67-2.61 (m, 1H), 2.28-2.21 (m, 1H), 1.86 (ddd, J = 14.2, 10.9, 7.8 Hz, 1H), 0.90 (s, 9H), 0.10 (s, 3H), 0.08 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ ppm 165.0, 134.0, 130.4, 130.3, 123.0, 122.9, 67.1, 45.5, 44.9, 41.3, 37.3, 25.8, 18.1, -4.7, -4.8. **IR** (neat) 2927, 2855, 1717, 1573, 1465, 1376, 1106, 1070, 913, 745 cm^{-1}. **ESMS** m/z 385.2 ($[M+H]^+$); **HRESMS** m/z calcd for $C_{21}H_{29}N_2O_3Si$ ($[M+H]^+$) 385.1947 found 385.1942. Stereochemistry confirmed by NOESY.

(**2.3r** *trans*): **^{1}H NMR** (400 MHz, $CDCl_3$) δ ppm 7.77 (dd, J = 5.4, 3.0 Hz, 2H), 7.68 (dd, J = 5.4, 3.0 Hz, 2H), 6.19 (ddd, J = 11.4, 4.8, 2.9 Hz, 1H), 5.83 (ddd, J = 11.4, 8.0, 3.5 Hz, 1H), 3.88 (dddd, J = 9.6, 9.5, 3.1, 3.1 Hz, 1H), 2.97-2.79 (m, 2H), 2.44-2.26 (m, 1H), 2.26-2.16 (m, 1H), 0.89 (s, 9H), 0.10 (s, 3H), 0.07 (s, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 165.0, 134.0, 131.6, 130.5, 124.5, 123.0, 68.4, 47.3, 47.1, 40.1, 38.3, 25.8, 18.1, -4.8, -4.9. **IR** (neat) 2958, 2859, 1713, 1659, 1642, 1378,1254,

1074, 913, 745 cm^{-1}. **ESMS** m/z 385.2 ($[M+H]^+$); **HRESMS** m/z calcd for $C_{21}H_{29}N_2O_3Si$ ($[M+H]^+$) 385.1947 found 385.1962.

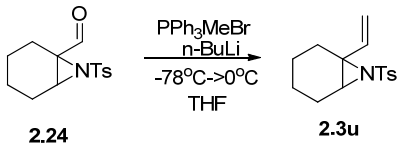


N-Phthalimido-7-azabicyclo[4.1.0]hept-2-ene (**2.3s**): Prepared according to general procedure B. Spectra matched existing literature data.[18]



trans-5-Isopropyl-2-methyl-N-phthalimido-7-aza-bicyclo[4.1.0]hept-2-ene (**2.3t**): (R)-(-)-α-Phellandrene (technical 65%) (0.135 g, 0.644 mmol, 1 equiv) was dissolved in dry CH_2Cl_2 (9.2 mL, 0.1 M) and N-amino-phthalimide (0.187 g, 1.15 mmol, 1.25 equiv.) was added. The heterogeneous solution was stirred vigorously while iodobenzenediacetate (0.326 g, 1.01 mmol, 1.1 equiv.) was added portion wise over 1 hour. The solution was stirred at room temperature for 14 hours. The reaction was diluted with CH_2Cl_2, washed with sat. $NaHCO_3$, and dried over Na_2SO_4. The solvent was evaporated and crude mixture purified by flash chromatography (R_f = 0.5, 20% ether:80% pentane) and then recrystallized from a solution of ether and pentane. Yield 20 mg (23%).

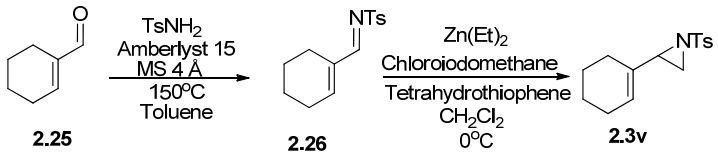
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.73 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.65 (dd, *J* = 5.4, 3.1 Hz, 2H), 5.62-5.53 (m, 1H), 2.95 (ddd, *J* = 7.7, 2.5, 1.1 Hz, 1H), 2.73 (d, *J* = 7.7 Hz, 1H), 2.25-2.17 (m, 1H), 2.15-2.07 (m, 1H), 2.06 (d, *J* = 1.85 Hz, 3H), 1.99-1.87 (m, 1H), 1.85-1.75 (m, 1H), 1.03 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 165.1, 134.0, 130.5, 129.6, 125.0, 122.9, 48.6, 44.6, 36.5, 31.3, 24.4, 21.7, 20.4, 20.3. **IR** (neat) 2956, 1714, 1684, 1653, 1635, 1616, 1558, 1507, 1457, 1419, 1374 cm^{-1}. **ESMS** m/z 297.2 ($[M+H]^+$); **HRESMS** m/z calcd for $C_{18}H_{21}N_2O_2$ ($[M+H]^+$) 297.1603 found 297.1601.



2.24 **2.3u**

N-Tosyl-1-vinyl-7-aza-bicyclo[4.1.0]heptane (**2.3u**): Methyltriphenylphosphonium bromide (0.256g, 0.72 mmol, 2 equiv.) was stirred under nitrogen in dry THF (4 mL) and cooled to -20 °C. A solution of potassium bis(trimethylsilyl)amide (0.5M in toluene, 1.4 mL, 0.72 mmol, 2 equiv.) was added dropwise and the resultant solution was stirred for 20 min. before addition of aziridino aldehyde[19] (0.1 g, 0.36 mmol, 1 equiv.) in 1 mL of THF. After 1 h at -20 °C the reaction was complete by TLC and was quenched with H_2O, extracted with ether, and dried with Na_2SO_4. The solvent was removed and the crude mixture purified by flash chromatography (R_f = 0.8, 30% ether: 70% pentanes). Yield 55 mg (55%).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.82 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 6.29 (dd, *J* = 17.4, 10.8 Hz, 1H), 5.47 (dd, *J* = 17.4, 0.7 Hz, 1H), 5.42 (dd, *J* = 10.8, 0.7 Hz, 1H), 3.28 (d, *J* = 5.4 Hz, 1H), 2.44 (s, 3H), 2.18 (ddd, *J* = 7.9, 4.7, 4.7 Hz, 1H), 1.96-1.88 (m, 1H), 1.88-1.81 (m, 1H), 1.64-1.56 (m, 1H), 1.51-1.32 (m, 3H), 1.18-1.07 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 143.5, 138.3, 136.1, 129.4, 127.1, 118.9, 53.5, 47.6, 26.6, 22.6, 21.6, 20.1, 19.0. **IR** (neat) 2939, 2864, 1326, 1154, 1090, 977, 933, 732, 659, 572 cm^{-1}. **ESMS** m/z 278.1 ($[M+H]^+$); **HRESMS** m/z calcd for $C_{15}H_{20}NO_2S$ ($[M+H]^+$) 278.1215 found 278.1215.



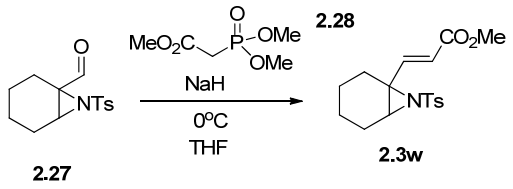
2.25 **2.26** **2.3v**

N-Cyclohexenylmethylen-4-methylbenzenesulfonamide: A mixture of 1-Cyclohexene-1-carboxaldehyde (0.10g, 0.91 mmol, 1 equiv.), p-toluenesulfonamide (0.155g, 0.91 mmol, 1 equiv.), activated MS 4A and catalytic amount of Amberlyst-15 in dry toluene (5 mL) was heated in a sealed tube for 12 h. The mixture was filtered through Celite and concentrated. The resulting yellow oil was used in the next reaction (mostly pure) or can be purified by silica gel flash chromatography (slightly unstable). Yield 215 mg (90%).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.40 (s, 1H), 7.72 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 6.75-6.71 (m, 1H), 2.33 (s, 3H), 2.29-2.20 (m, 2H), 2.19-2.13 (m, 2H), 1.59-1.50 (m, 4H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 172.3, 153.8, 144.1, 137.2, 135.6, 129.6, 127.8, 27.3, 22.7, 21.6, 21.5, 21.2. **IR** (neat) 2934, 2863, 1628, 1567, 1319, 1158, 1090, 930, 807, 777, 696, 655, 568 cm^{-1}. **ESMS** m/z 264.1 ($[M+H]^+$); **HRESMS** m/z calcd for $C_{14}H_{18}NO_2S$ ($[M+H]^+$) 264.1058 found 264.1058.

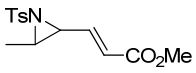
2-Cyclohexenyl-N-tosylaziridine (**2.3v**): Diethyl zinc (1.0 M in Hexanes, 0.4 ml, 0.4 mmol, 2.1 equiv.) was added to a stirred solution of chloroiodomethane (62 mg, 0.34 mmol, 2 equiv.) in 2 mL of dry CH_2Cl_2 under N_2 at 0 ^oC. The solution is stirred for 10 min. then tetrahydrothiophene is added (46 mg, 0.52 mmol, 3 equiv.). Lastly, the imine (**2.26**, 46 mg, 0.17 mmol, 1 equiv.) was added and reaction is warmed to RT slowly over 4 h. The reaction is quenched with sat. $Na_2S_2O_3$ and extracted with CH_2Cl_2. The solution is dried with Na_2SO_4, solvent removed and purified by flash chromatography (R_f = 0.6, 20% ether: 80% pentanes). Yield 36 mg (75%).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.83 (d, *J* = 8.2 Hz, 2H), 7.33 (d, *J* = 8.2 Hz, 2H), 5.82-5.77 (m, 1H), 3.24 (dd, *J* = 7.0, 4.8 Hz, 1H), 2.64 (d, *J* = 7.0 Hz, 1H), 2.45 (s, 3H), 2.30 (d, *J* = 4.8 Hz, 1H), 2.03-1.93 (m, 2H), 1.91-1.62 (m, 2H), 1.63-1.47 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 144.3, 135.2, 131.4, 129.6, 127.9, 127.8, 43.9, 32.1, 25.1, 23.9, 22.0, 21.7. **IR** (neat) 2927, 2859, 1597, 1449, 1323, 1160, 1094, 958, 902, 815, 718, 669, 572 cm^{-1}. **ESMS** m/z 278.1 ($[M+H]^+$); **HRESMS** m/z calcd for $C_{15}H_{20}NO_2S$ ($[M+H]^+$) 278.1215 found 278.1206.



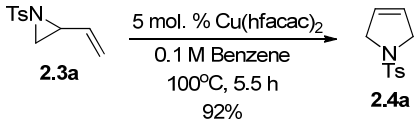
(E)-Methyl-3-(N-tosyl-7-aza-bicyclo[4.1.0]heptan-1-yl)acrylate (**2.3w**): Trimethyl phosphonoacetate (32 mg, 0.18 mmol, 2 equiv.) was stirred under nitrogen in dry THF (4 mL) and cooled to 0 ^oC. NaH (7 mg, 0.18 mmol, 2 equiv., 60% dispersion in mineral oil) was added to the solution and stirred for 5 min. The aziridino aldehyde[20] (0.025 g, 0.09 mmol, 1 equiv.) in 1 mL of THF was added slowly. The solution is warmed to room temperature overnight then quenched with H_2O and extracted with CH_2Cl_2. The solution was dried with Na_2SO_4 and the solvent removed. The crude mixture is purified by flash chromatography (R_f = 0.2, 30% ether: 70% pentanes). Yield 28 mg (95%, E:Z = 7:1).

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.82 (d, *J* = 8.4 Hz, 2H), 7.33 (d, *J* = 8.4 Hz, 2H), 7.27 (d, *J* = 15.9 Hz, 1H), 6.12 (d, *J* = 15.9 Hz, 1H), 3.79 (s, 3H), 3.38 (d, *J* = 5.3 Hz, 1H), 2.46 (s, 3H), 2.25-2.08 (m, 1H), 2.04-1.91 (m, 1H), 1.90-1.77 (m, 1H), 1.76-1.63 (m, 1H), 1.56-1.36 (m, 3H), 1.23-1.05 (m, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 166.0, 145.2, 144.0, 137.4, 129.5, 127.3, 124.2, 51.8, 51.3, 48.0, 26.6, 22.6, 21.6, 19.8, 18.8. **IR** (neat) 2945, 2862, 1724, 1650, 1597, 1436, 1313, 1154, 1090, 981, 929, 668, 583 cm^{-1}. **ESMS** m/z 336.1 ($[M+H]^+$); **HRESMS** m/z calcd for $C_{17}H_{22}NO_4S$ ($[M+H]^+$) 336.1270 found 336.1267.



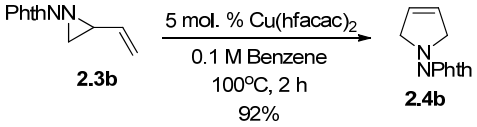
(E)-Methyl-3-(3-methyl-1-tosylaziridin-2-yl)acrylate (**2.3x**): Prepared according to existing literature procedure and spectra matched existing literature data.[21]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.3, 1H), 7.32 (d, *J* = 8.4, 1H), 6.83 (dd, *J* = 15.6, 8.7, 1H), 6.06 (d, *J* = 15.6, 1H), 4.18 (qd, *J* = 7.1, 2.1, 1H), 3.20 (dd, *J* = 8.7, 4.1, 1H), 3.00 (dd, *J* = 5.8, 4.2, 1H), 2.44 (s, 2H), 1.55 (d, *J* = 5.9, 2H), 1.28 (t, *J* = 7.1, 2H).



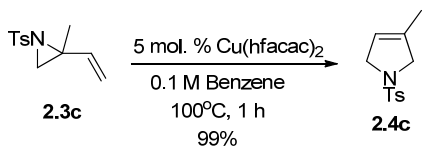
1-Tosyl-2,5-dihydro-1H-pyrrole (**2.4a**): Prepared according to general procedure A. Spectra matched existing literature data.[22]

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 – 7.69 (m, 2H), 7.31 (d, *J* = 8.3, 2H), 5.65 (s, 2H), 4.11 (s, 4H), 2.42 (s, 3H).



N-Phthalimido-2,5-dihydro-1H-pyrrole (**2.4a**): Prepared according to general procedure A.

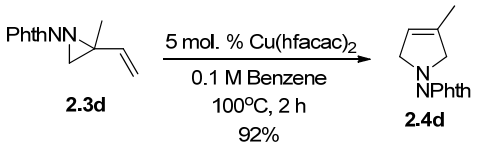
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.85 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.74 (dd, *J* = 5.4, 3.1 Hz, 2H), 5.87 (s, 2H), 4.19 (s, 4H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 167.2, 134.3, 130.2, 126.3, 123.3, 59.7. **IR** (neat) 2907, 2849, 1708, 1614, 1466, 1380, 1123, 1010, 881, 713, 523 cm^{-1}. **ESMS** m/z 237.1 ($[M+Na]^+$); **HRESMS** m/z calcd for $C_{12}H_{10}N_2O_2Na$ ($[M+Na]^+$) 237.0640 found 237.0646.



3-Methyl-1-tosyl-2,5-dihydro-1H-pyrrole (**2.4c**): Prepared according to general procedure A. Spectra matched existing literature data.[23]

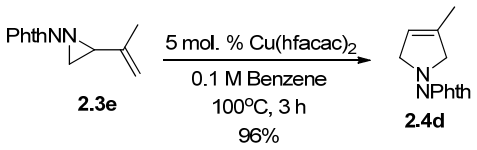
^{1}H NMR (400 MHz, $CDCl_3$): δ ppm 1.66 (mc, 3H), 2.43 (s, 3H), 3.95–3.98 (m, 2H), 4.05–4.09 (m, 2H), 5.25 (mc, 1H), 7.32 (m, 2H), 7.72 (m, 2H); **^{13}C NMR** (100.6

MHz, $CDCl_3$): δ ppm 14.1, 21.5, 55.1,57.7, 119.1, 127.5, 129.7, 134.4, 135.1, 143.3; **GC/MS–EI** (70 eV); m/z (%) = 237 (22) [M+].



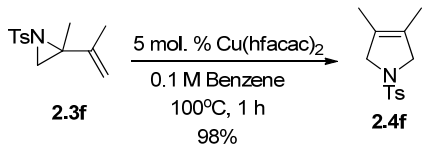
3-Methyl-N-Phthalimido-2,5-dihydro-1H-pyrrole (**2.4d**): Prepared according to general procedure A.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.85 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.73 (dd, *J* = 5.4, 3.1 Hz, 2H), 5.46 (s, 1H), 4.17 (bs, 2H), 4.08 (bs, 2H), 1.77 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 167.2, 135.8, 134.3, 130.4, 123.3, 120.0, 62.4, 60.1, 14.6. IR (neat) 2965, 2853, 1783, 1723, 1382, 1202, 1117, 1052, 913, 885, 712, 523 cm^{-1}. **ESMS** m/z 251.1 ($[M+Na]^+$); **HRESMS** m/z calcd for $C_{13}H_{12}N_2O_2Na$ ($[M+Na]^+$) 251.0796 found 251.0805.

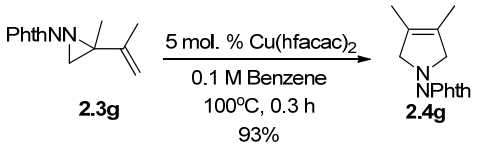


3-Methyl-N-phthalimido-2,5-dihydro-1H-pyrrole (**2.4d**): Prepared according to general procedure A.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.85 (dd, *J* = 5.4, 3.1 Hz, 2H), 7.73 (dd, *J* = 5.4, 3.1 Hz, 2H), 5.46 (s, 1H), 4.17 (bs, 2H), 4.08 (bs, 2H), 1.77 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 167.2, 135.8, 134.3, 130.4, 123.3, 120.0, 62.4, 60.1, 14.6. IR (neat) 2965, 2853, 1783, 1723, 1382, 1202, 1117, 1052, 913, 885, 712, 523 cm^{-1}. **ESMS** m/z 251.1 ($[M+Na]^+$); **HRESMS** m/z calcd for $C_{13}H_{12}N_2O_2Na$ ($[M+Na]^+$) 251.0796 found 251.0805.



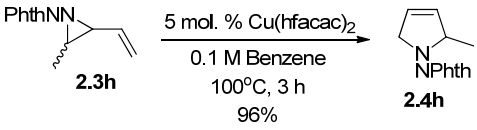
3,4-Dimethyl-1-tosyl-2,5-dihydro-1H-pyrrole (**2.4f**): Prepared according to general procedure A. Spectra matched existing literature data.[24]



2.3g **2.4g**

3,4-Dimethyl-N-(phthalamido)-3-pyrroline (**2.4g**): Prepared according to general procedure A.

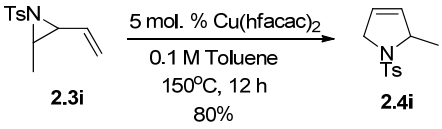
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.84 (dd, *J* = 5.6, 3.0 Hz, 2H), 7.73 (dd, *J* = 5.6, 3.0 Hz, 2H), 4.08 (s, 4H), 1.65 (s, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 167.3, 134.2, 130.3, 126.9, 123.3, 63.7, 11.4. **IR** (neat) 2884, 2849, 1727, 1381, 1207, 1118, 1061, 913, 744, 711 cm^{-1}. **ESMS** m/z 265.1 ($[M+Na]^+$); **HRESMS** m/z calcd for $C_{14}H_{14}N_2O_2Na$ ($[M+Na]^+$) 265.0953 found 265.0963.



2.3h **2.4h**

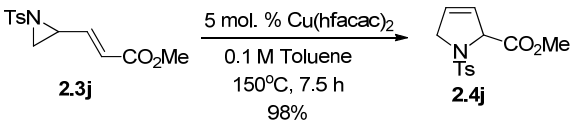
2-Methyl-N-(phthalamido)-3-pyrroline (**2.4h**): Prepared according to general procedure A.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.84 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.73 (dd, *J* = 5.5, 3.0 Hz, 2H), 5.82 (ddd, *J* = 6.3, 4.1, 2.1 Hz, 1H), 5.74 (tdd, *J* = 6.7, 2.4, 1.8, 1.8 Hz, 1H), 4.58-4.48 (m, 1H), 4.28 (dddd, *J* = 12.8, 4.4, 2.5, 1.8 Hz, 1H), 4.08 (tdd, *J* = 12.8, 5.1, 2.0, 2.0 Hz, 1H), 1.21 (d, *J* = 6.5 Hz, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 167.5, 134.2, 131.7, 130.1, 125.4, 123.3, 65.3, 59.0, 20.3. **IR** (neat) 2972.6, 2848, 1738, 1723, 1378, 1203, 882, 713 cm^{-1}. **ESMS** m/z 251.1 ($[M+Na]^+$); **HRESMS** m/z calcd for $C_{13}H_{12}N_2O_2Na$ ($[M+Na]^+$) 251.0796 found 251.0785.



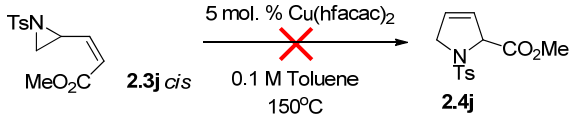
2.3i **2.4i**

2-Methyl-1-tosyl-2,5-dihydro-1H-pyrrole (**2.4i**): Prepared according to general procedure A. Spectra matched existing literature data.[25]

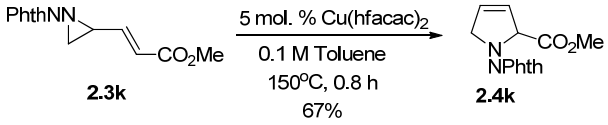


2.3j **2.4j**

Methyl 1-tosyl-2,5-dihydro-1H-pyrrole-2-carboxylate (**2.4j**): Prepared according to general procedure A. Spectra matched existing literature data.[26]

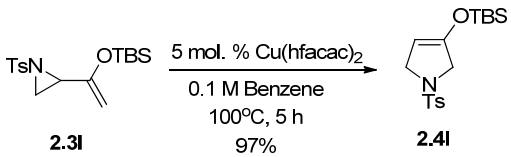


Methyl-N-phthalimido-2-carboxylate-3-pyrroline (**2.4j**): General procedure A did not furnish product but slowly decomposed starting material over time.



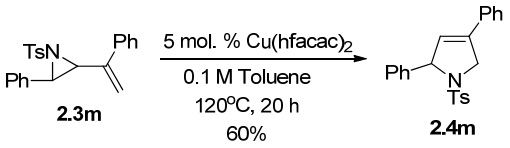
Methyl-N-phthalimido-2-carboxylate-3-pyrroline (**2.4k**): Prepared according to general procedure A.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.87 (dd, *J* = 5.5, 3.1 Hz, 2H), 7.75 (dd, *J* = 5.5, 3.1 Hz, 2H), 6.01 (ddd, *J* = 6.6, 4.5, 2.0 Hz, 1H), 5.94 (dddd, *J* = 6.6, 2.2, 2.1, 2.0 Hz, 1H), 5.19 (ddd, *J* = 7.4, 5.1, 2.3 Hz, 2H), 4.26-4.23 (m, 1H), 3.73 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 171.0, 166.7, 134.4, 130.1, 128.4, 125.2, 123.5, 71.0, 60.2, 52.4. **IR** (neat) 2952, 2862, 1787, 1725, 1467, 1382, 1204, 1121, 886, 715, 618, 523 cm^{-1}. **ESMS** m/z 295.1 ($[M+Na]^+$); **HRESMS** m/z calcd for $C_{14}H_{12}N_2O_4Na$ ($[M+Na]^+$) 295.0695 found 295.0701.



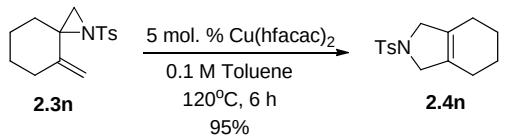
3-(t-Butyldimethylsiloxy)-N-tosyl-3-pyrroline (**2.4l**): Prepared according to general procedure A.

^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 7.71 (d, *J* = 8.2 Hz, 2H), 7.32 (d, *J* = 8.2 Hz, 2H), 4.51 (m, 1H), 4.08-4.00 (m, 2H), 3.92-3.84 (m, 2H), 2.42 (s, 3H), 0.86 (s, 9H), 0.10 (s, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 148.6, 143.4, 133.9, 129.7, 127.5, 96.7, 53.1, 52.4, 25.4, 21.5, 18.0, -4.9. **IR** (neat) 2955, 2930, 2859, 1662, 1349, 1265, 1165, 842, 669, 549 cm^{-1}. **ESMS** m/z 354.1 ($[M+H]^+$); **HRESMS** m/z calcd for $C_{17}H_{28}NO_3SiS$ ($[M+H]^+$) 354.1559 found 354.1570.



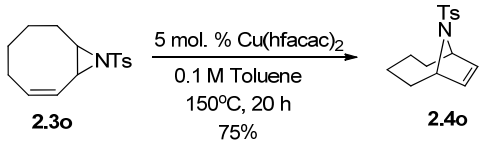
2,4-Diphenyl-N-tosyl-3-pyrroline (**2.4m**): Prepared according to general procedure A.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.55 (d, *J* = 8.2 Hz, 2H), 7.35-7.33 (m, 1H), 7.33 (bs, 3H), 7.32-7.25 (m, 6H), 7.19 (d, *J* = 8.2 Hz, 2H), 6.01 (dd, *J* = 2.0, 2.0, 1H), 5.66 (ddd, *J* = 5.1, 2.5, 2.5 Hz, 1H), 4.74-4.61 (m, 2H), 2.37 (s, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 143.2, 140.5, 136.2, 135.3, 132.3, 129.5, 128.6, 128.7, 128.5, 127.9, 127.4, 127.2, 125.6, 124.0, 71.0, 55.4, 21.5. **IR** (neat) 3061, 3030, 2920, 2863, 1598, 1495, 1450, 1347, 1163, 1098, 752, 665, 599, 547 cm^{-1}. **ESMS** m/z 376.1($[M+H]^+$); **HRESMS** m/z calcd for $C_{23}H_{22}NO_2S$ ($[M+H]^+$) 376.1371 found 376.1364.



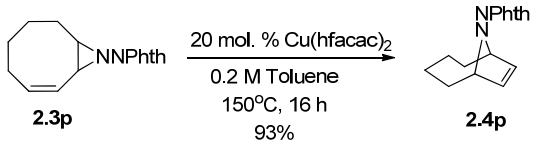
2-Tosyl-2,3,4,5,6,7-hexahydro-1H-isoindole (**2.4n**): Prepared according to general procedure A. Spectra matched existing literature data.[27]

m.p. 133-134 °C. **IR** (nujol) 1340, 1162, 1099, 718 and 663 cm^{-1}. **^{1}H NMR** (250 MHz, $CDCl_3$) δ ppm 7.72 (2 H, d, J8.4, ArH), 7.32 (2 H, d, J8.4, ArH), 3.96 (4 H, s, 1-H, and 3-H,), 2.43 (3 H, s, CH,), 2.0-1.8 (4 H, m, 2 x CH,) and 1.7-1.5 (4 H, m, 2 x CH,); **^{13}C NMR** (62.9 MHz, $CDCl_3$) δ ppm 143.2 , 134.5, 129.7, 127.6, 122.6, 57.1, 22.8, 22.1, 21.5. **EIMS** ; m/z 277 (M+), 155, 122, 91, 65, 41, 35.



N-Tosyl-9-aza-bicyclo[4.2.1]non-7-ene (**2.4o**): Prepared according to general procedure A. The $Cu(hfacac)_2$ must be scrupulously dried prior to use.

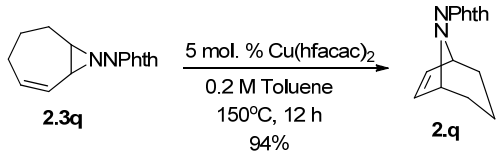
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.65 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 5.50 (d, *J* = 1.1 Hz, 2H), 4.69 (td, *J* = 6.3, 1.1, 2H), 2.39 (s, 3H), 2.02-1.92 (m, 2H), 1.80-1.64 (m, 2H), 1.61-1.43 (m, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 142.9, 136.1, 130.8, 129.3, 127.0, 64.6, 33.1, 24.2, 21.5 cm^{-1}. **IR** (neat) 2924, 2852, 1596, 1337, 1298, 1159, 1104, 1044, 822, 666, 606 cm^{-1}. **ESMS** m/z 278.1 ($[M+H]^+$); **HRESMS** m/z calcd for $C_{15}H_{20}NO_2S$ ($[M+H]^+$) 278.1215 found 278.1222.



2.3p **2.4p**

N-Phthalimido-9-aza-bicyclo [4.2.1] non-7-ene (**2.4p**): Prepared according to general procedure A.

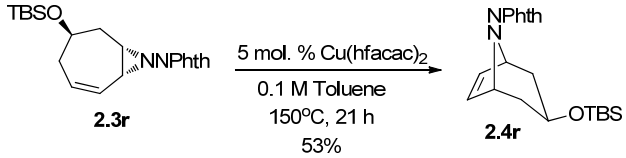
^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.78 (dd, J = 5.4, 3.1 Hz, 2H), 7.69 (dd, J = 5.4, 3.1 Hz, 2H), 5.97 (d, J = 0.9 Hz, 2H), 4.17 (d, J = 6.5 Hz, 2H), 1.97 (ddd, J = 12.9, 11.9, 6.5 Hz, 2H), 1.93-1.85 (m, 2H), 1.64-1.47 (m, 2H), 1.44-1.35 (m, 2H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 167.3, 134.0, 131.8, 130.2, 123.0, 72.1, 32.4, 24.4. **IR** (neat) 2920, 2853, 1725, 1374, 1202, 1079, 913, 745, 711, 673 cm^{-1}. **ESMS** m/z 291.1 ($[M+Na]^+$); **HRESMS** m/z calcd for $C_{16}H_{16}N_2O_2Na$ ($[M+Na]^+$) 291.1109 found 2791.1114.



2.3q **2.q**

N-Phthalimido-8-aza-bicyclo [3.2.1] oct-6-ene (**2.4q**): Prepared according to general procedure A.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.76-7.71 (m, 2H), 7.68-7.63 (m, 2H), 6.14 (bs, 2H), 4.27 (bs, 2H), 2.13-2.02 (m, 2H), 1.51-1.42 (m, 4H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 166.2, 133.8, 130.4, 129.8, 122.8, 68.0, 26.0, 15.9. **IR** (neat) 2936, 1772, 1713, 1371, 1318, 1118, 1043, 876, 707 cm^{-1}. **ESMS** m/z 277.1 ($[M+Na]^+$); **HRESMS** m/z calcd for $C_{15}H_{14}N_2O_2Na$ ($[M+Na]^+$) 277.0953 found 277.0952.

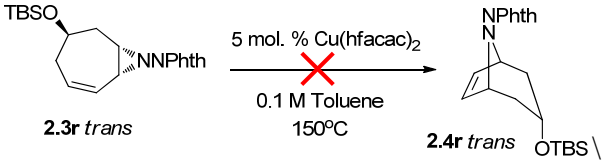


2.3r **2.4r**

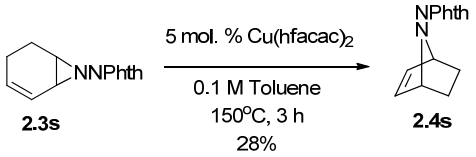
3-(tert-Butyldimethylsilyloxy)-N-phthalimido-8-aza-bicyclo [3.2.1] oct-6-ene (**2.4r**): Prepared according to general procedure A.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.73 (dd, *J* = 5.6, 3.0 Hz, 2H), 7.65 (dd, *J* = 5.6, 3.0 Hz, 2H), 6.15-6.12 (m, 2H), 4.34 (dd, *J* = 2.8, 2.8 Hz, 2H), 3.84 (m, 1H), 2.04 (ddd, *J* = 12.3, 9.3, 2.8 Hz, 2H), 1.92 (ddd, *J* = 13.5, 6.8, 3.2, Hz, 2H), 1.90 (dd, *J* = 6.8, 3.2 Hz, 1H), 0.86 (s, 9H), 0.00 (s, 6H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 166.0, 133.8, 130.4, 130.3, 122.8, 66.7, 65.1, 36.0, 25.8, 25.6, 18.0, -4.7. **IR** (neat) 2925, 2855, 1725, 1584, 1443, 1380, 1238, 1173, 1107, 913, 744 cm^{-1}. **ESMS** m/z

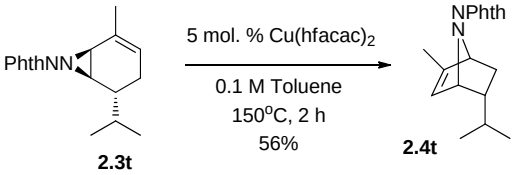
385.2 ([M+H]$^+$); **HRESMS** m/z calcd for $C_{21}H_{29}N_2O_3Si$([M+H]$^+$) 385.1947 found 385.1952. Stereochemistry confirmed by NOESY.



trans-3-(tert-Butyldimethylsilyloxy)-N-phthalimido-8-aza-bicyclo [3.2.1] oct-6-ene (**2.4r** *trans*): General procedure A did not furnish product but slowly decomposed starting material over time.

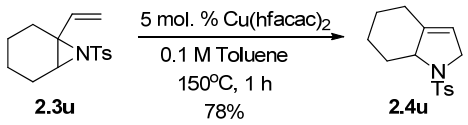


N-Phthalimido-7-azabicyclo[2.2.1]hept-2-ene (**2.4s**): Prepared according to general procedure A. Spectra matched existing literature data.[28]



(1R,2R,4S)-2-Isopropyl-5-methyl-N-phthalimido-7-azabicyclo[2.2.1]hept-5-ene (**2.4t**): Prepared according to general procedure A.

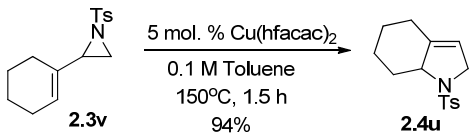
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.70 (dd, *J* = 5.5, 3.0 Hz, 2H), 7.62 (dd, *J* = 5.5, 3.0 Hz, 2H), 5.60-5.53 (m, 1H), 4.71-4.65 (m, 1H), 2.17-2.07 (m, 1H), 2.04-1.95 (m, 1H), 1.88 (d, *J* = 1.7 Hz, 3H), 1.03-0.92 (m, 1H), 0.91 (d, *J* = 5.8 Hz, 3H), 0.85 (d, *J* = 6.1 Hz, 3H), 0.72 (dd, *J* = 11.3, 4.3 Hz, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 166.1, 145.7, 133.6, 130.6, 122.6, 122.0, 69.6, 69.0, 45.2, 32.4, 28.3, 21.4, 21.0. **IR** (neat) 2958, 1717, 1684, 1653, 1558, 1507, 1457, 1375, 1260, 750 cm^{-1}. **ESMS** m/z 297.2 ([M+H]$^+$); **HRESMS** m/z calcd for $C_{18}H_{21}N_2O_2$ ([M+H]$^+$) 297.1603 found 297.1596.



2.3u **2.4u**

N-Tosyl-2,4,5,6,7,7a-hexahydro-1H-indole (**2.4u**): Prepared according to general procedure A.

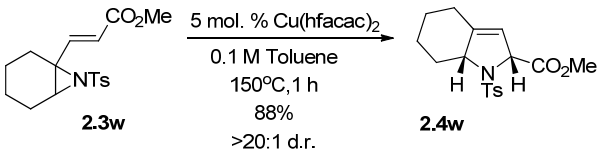
^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.73 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 5.15 (bs, 1H), 4.16-4.07 (m, 1H), 4.02-3.97 (m, 2H), 2.53-2.46 (m, 1H), 2.43 (s, 3H), 2.43-2.39 (m, 1H), 1.90-1.73 (m, 3H), 1.44-1.31 (m, 1H), 1.23-1.14 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 143.2, 141.7, 134.8, 129.6, 127.5, 114.1, 66.4, 54.8, 36.4, 28.3, 26.4, 23.9, 21.5. **IR** (neat) 2994, 2858, 1598, 1447, 1344, 1163, 1100, 1068, 1043, 815, 675, 589, 550 cm^{-1}. **ESMS** m/z 278.1 ($[M+H]^+$); **HRESMS** m/z calcd for $C_{15}H_{20}NO_2S$ ($[M+H]^+$) 278.1215 found 278.1214.



2.3v **2.4u**

N-Tosyl-2,4,5,6,7,7a-hexahydro-1H-indole (**2.4u**): Prepared according to general procedure A.

^{1}H NMR (600 MHz, $CDCl_3$) δ ppm 7.73 (d, *J* = 8.0 Hz, 2H), 7.32 (d, *J* = 8.0 Hz, 2H), 5.15 (bs, 1H), 4.16-4.07 (m, 1H), 4.02-3.97 (m, 2H), 2.53-2.46 (m, 1H), 2.43 (s, 3H), 2.43-2.39 (m, 1H), 1.90-1.73 (m, 3H), 1.44-1.31 (m, 1H), 1.23-1.14 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 143.2, 141.7, 134.8, 129.6, 127.5, 114.1, 66.4, 54.8, 36.4, 28.3, 26.4, 23.9, 21.5. **IR** (neat) 2994, 2858, 1598, 1447, 1344, 1163, 1100, 1068, 1043, 815, 675, 589, 550 cm^{-1}. **ESMS** m/z 278.1 ($[M+H]^+$); **HRESMS** m/z calcd for $C_{15}H_{20}NO_2S$ ($[M+H]^+$) 278.1215 found 278.1214.

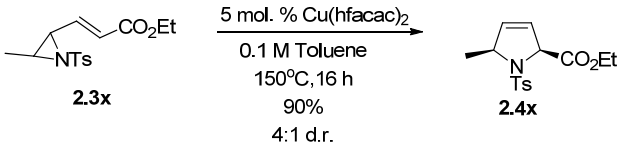


2.3w **2.4w**

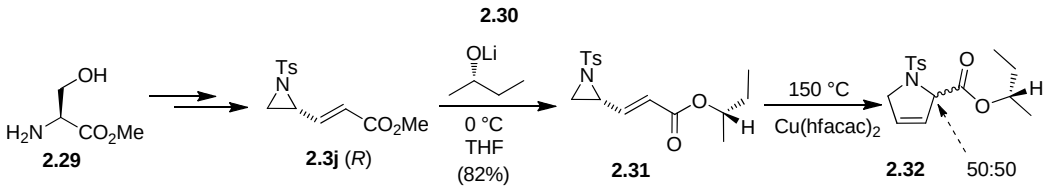
Methyl-N-tosyl-2,4,5,6,7,7a-hexahydro-1H-indole-2-carboxylate (± **2.4w**): Prepared according to general procedure A.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.75 (d, *J* = 8.2 Hz, 2H), 7.29 (d, *J* = 8.2 Hz, 2H), 5.13 (dd, *J* = 2.0, 1.9 Hz, 1H), 4.97 (ddd, *J* = 3.3, 2.1, 2.0 Hz, 1H), 4.09-3.98 (m, 1H), 3.73 (s, 3H), 2.40 (s, 3H), 2.39-2.35 (m, 1H), 2.35-2.26 (m, 1H), 1.95-1.80 (m, 1H), 1.80-1.71 (m, 2H), 1.54-1.41 (m, 1H), 1.39-1.12 (m, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 170.9, 145.3, 143.6, 135.5, 129.7, 127.6, 113.6, 68.0, 67.2, 52.6, 36.4, 28.3,

26.3, 23.7, 21.6. **IR** (neat) 2940, 2861, 1760, 1737, 1436, 1349, 1276, 1164, 1100, 913, 748, 593 cm^{-1}. **ESMS** m/z 336.1 ($[M+H]^+$); **HRESMS** m/z calcd for $C_{17}H_{22}NO_4S$ ($[M+H]^+$) 336.1270 found 336.1269.



cis-Methyl 5-methyl-1-tosyl-2,5-dihydro-1H-pyrrole-2-carboxylate (± **2.4x**): Prepared according to general procedure A. Spectra matched existing literature data.[29]



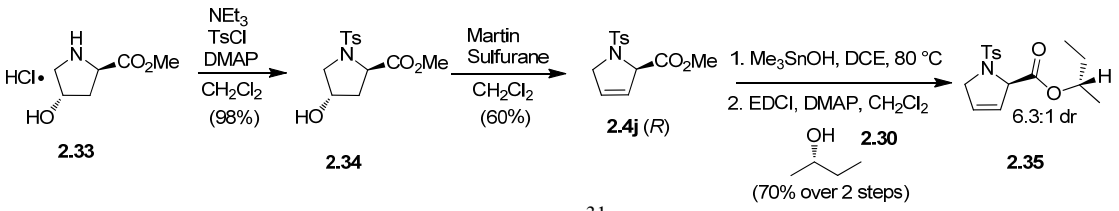
(E)-(S)-sec-Butyl 3-((R)-1-tosylaziridin-2-yl)acrylate (**2.31**): A solution of *n*-BuLi in hexanes (1.57 M, 290 µL, 0.45 mmol, 2.5 equiv.) was added drop wise to a solution of (*S*)-2-butanol (41 µL, 0.45 mmol) in THF (1.5 mL) at 0 °C. After stirring for 15 min the solution was cooled to -78 °C and to it was added **2.3j** (*R*)[30] (substrate 10) (50 mg, 0.18 mmol, 1 equiv.) in THF (1.5 mL). The reaction was warmed to 0 °C, stirred for 45 min, and poured into a separatory funnel containing Et_2O and H_2O. The crude material was extracted with Et_2O, washed with H_2O and brine, dried over Na_2SO_4, and evaporated to dryness. Flash chromatography (R_f = 0.45, 30% EtOAc:70% hexanes) afforded vinylaziridine **2.31** as a 8:1 mixture of diastereomers. Yield 48 mg (82%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.82 (d, *J* = 8.2 Hz, 2H), 7.35 (d, *J* = 8.2 Hz, 2H), 6.53 (dd, *J* = 15.6, 7.5 Hz, 1H), 6.10 (d, J=15.6 Hz, 1H), 4.87 (tq, *J* = 13.4, 6.3, Hz, 1H), 3.36 (ddd, *J* = 7.5, 7.2, 4.2 Hz, 1H), 2.86 (d, *J* = 7.2 Hz, 1H), 2.45 (s, 3H), 2.27 (d, *J* = 4.2 Hz, 1H), 1.57 (dq, *J* = 13.4, 7.4 Hz, 2H), 1.21 (d, *J* = 6.3 Hz, 3H), 0.88 (t, *J* = 7.4 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ ppm 164.9, 144.9, 141.2, 134.5, 129.8, 127.9, 125.8, 72.7, 38.5, 34.6, 28.7, 21.6, 19.3, 9.6. **IR** (neat) 2974, 2936, 1714, 1659, 1328, 1163, 1091, 980, 869, 816, 689, 569 cm^{-1}. **ESMS** m/z 346.1 ($[M+Na]^+$); **HRESMS** m/z calcd for $C_{16}H_{21}NO_4SNa$ ($[M+Na]^+$) 346.1089 found 346.1087.

(S)-((S) sec-Butyl)-N-tosyl-2,5-dihydro-1H-pyrrole-2-carboxylate (**2.32**): Prepared according to general procedure A.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.80 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 5.84 (m, 1H), 5.66 (m, 1H), 5.10 (m, 1H), 4.98-4.84 (m, 1H), 4.21-4.15 (m, 2H), 2.42 (s, 3H), 1.68-1.49 (m, 2H), 1.25 (d, *J* = 6.3 Hz, 3H), 0.90 (t, *J* = 7.5 Hz, 3H). **^{13}C**

NMR (125 Mhz, $CDCl_3$) δ ppm 169.4, 143.7, 135.3, 129.7, 128.3, 127.5, 127.5, 124.9, 73.9, 68.4, 55.0, 28.7, 21.6, 19.4, 9.6 cm^{-1}. **IR** (neat) 294, 2934, 1752, 1728, 1598, 1454, 1351, 1165, 1110, 817, 671, 598, 549 cm^{-1}. **ESMS** m/z 346.1 ($[M+Na]^+$); **HRESMS** m/z calcd for $C_{16}H_{21}NO_4SNa$ ($[M+Na]^+$) 346.1089 found 346.1096.



N-Tosyl hydroxyproline methyl ester (**2.34**)**:**[31] To a suspension of *L*-hydroxyproline methyl ester hydrochloride (350 mg, 1.9 mmol, 1 equiv.) in CH_2Cl_2 (10 mL) was added triethylamine (1.34 mL, 9.5 mmol, 5 equiv.) at 0 °C. The solution was stirred for 10 minutes at which point *p*-toluenesulfonyl chloride (725 mg, 3.8 mmol, 2 equiv.) in CH_2Cl_2 (10 mL) was added, followed by DMAP (24 mg, 0.20 mmol, 0.1 equiv.). The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The solution was poured over EtOAc and washed with aqueous NH_4Cl (sat.) and brine. The organic layer was dried over anhydrous Na_2SO_4, evaporated to dryness, and purified by flash chromatography. Yield: 565 mg (98%).

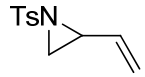
N-Tosyl dehydroproline methyl ester (**2.4j** (*R*))**:**[32] To a solution of *N*-tosyl hydroxyproline methyl ester (50 mg, 0.17 mmol, 1 equiv.) in CH_2Cl_2 (2 mL) was added Martin Sulfurane dehydrating reagent (343 mg, 0.51 mmol, 3 equiv.) at 0 °C. After stirring for 1 h the reaction solvent was removed by rotary evaporation and the remaining residue was purified by flash chromatography. Yield 28.2 mg (60%).

N-Tosyl Dehydroproline (S)-2-Butanol Ester (**2.35**):[33] *N*-Tosyl dehydroproline methyl ester **2.4j** (*R*) (14 mg, 0.05 mmol, 1 equiv.) and trimethyltin hydroxide (45 mg, 0.25 mmol, 5 equiv.) were dissolved in DCE (500 μL) and heated to 80 °C for 3 h in a sealed tube. The solvent was removed by rotary evaporation and the remaining residue was dissolved in EtOAc (2 mL) and washed with 5% aqueous HCl (3x). The solution was dried over Na_2SO_4 and concentrated by rotary evaporation. The crude hydrolysis product was immediately dissolved in CH_2Cl_2 (500 μL) and cooled to 0 °C. (*S*)-2-Butanol (40 μL, 0.43 mmol, 8.5 equiv.), EDCI (11.5 mg, 0.06 mmol, 1.2 equiv), and DMAP (0.3 mg, 0.005 mmol. 0.1 equiv) were added sequentially. The reaction mixture was warmed to room temperature and stirred overnight. It was diluted with CH_2Cl_2 and washed with H_2O, brine, and dried over Na_2SO_4. Purification by flash chromatography (R_f = 0.40, 30% EtOAc:70% hexanes) afforded *N*-tosyl dehydroproline (*S*)-2-butanol ester as a 6.3:1 mixture of diastereomers. Yield: 12.0 mg (70% from **2.4j** (*R*)).

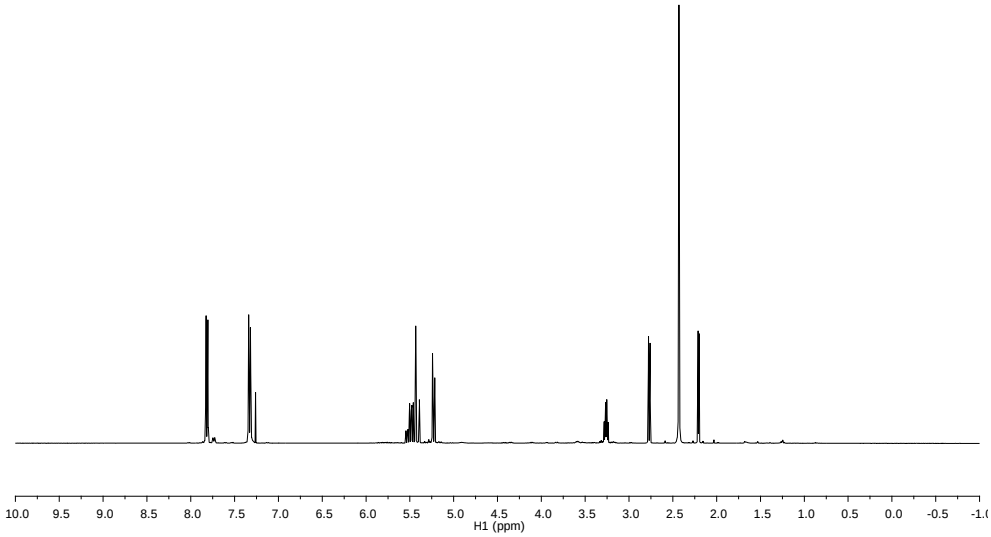
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.80 (d, *J* = 8.2 Hz, 2H), 7.31 (d, *J* = 8.2 Hz, 2H), 5.84 (m, 1H), 5.66 (m, 1H), 5.10 (m, 1H), 4.98-4.84 (m, 1H), 4.21-4.15 (m, 2H), 2.42 (s, 3H), 1.68-1.49 (m, 2H), 1.25 (d, *J* = 6.3 Hz, 3H), 0.90 (t, *J* = 7.5 Hz, 3H). **^{13}C**

NMR (125 MHz, $CDCl_3$) δ ppm 169.4, 143.7, 135.3, 129.7, 128.3, 127.5, 127.5, 124.9, 73.9, 68.4, 55.0, 28.7, 21.6, 19.4, 9.6 cm^{-1}. **IR** (neat) 294, 2934, 1752, 1728, 1598, 1454, 1351, 1165, 1110, 817, 671, 598, 549 cm^{-1}. **ESMS** m/z 346.1 ($[M+Na]^+$); **HRESMS** m/z calcd for $C_{16}H_{21}NO_4SNa$ ($[M+Na]^+$) 346.1089 found 346.1096.

A2.2 ^{1}H and ^{13}C NMR Spectra for Chapter 2

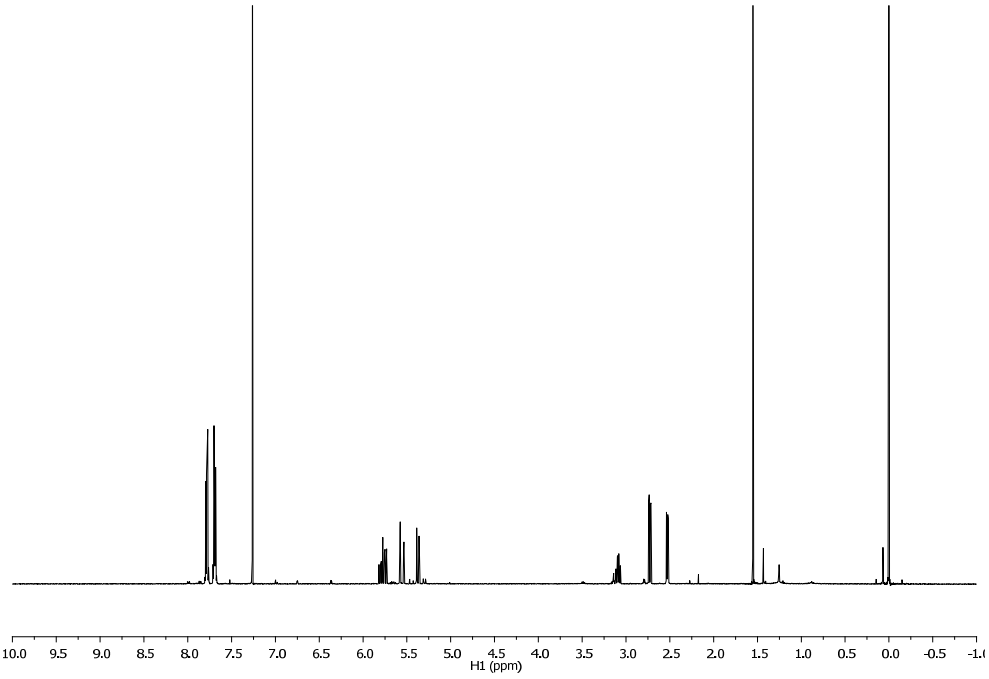


2.3a




PhthNN

2.3b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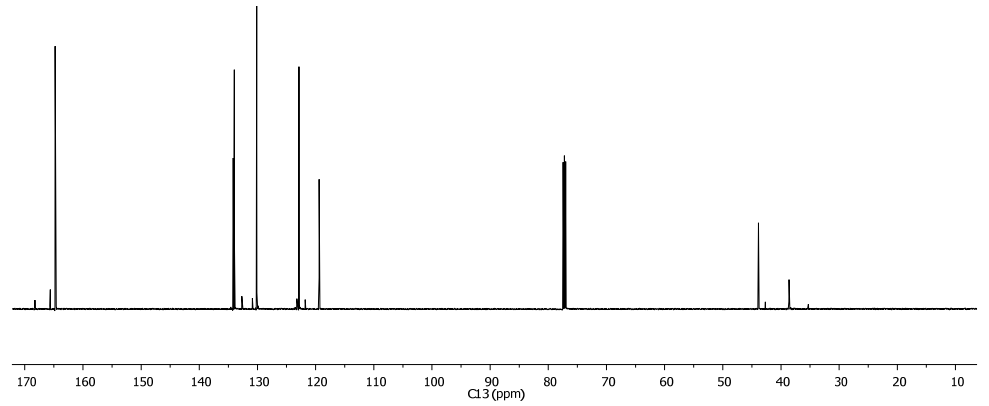
H1 (ppm)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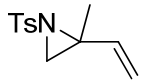
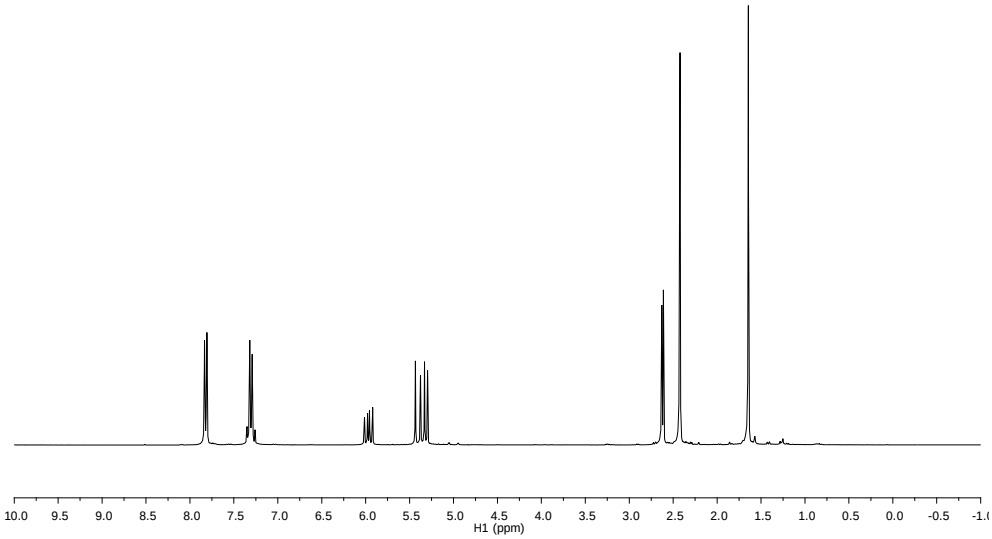
C13 (ppm)


TsN

2.3c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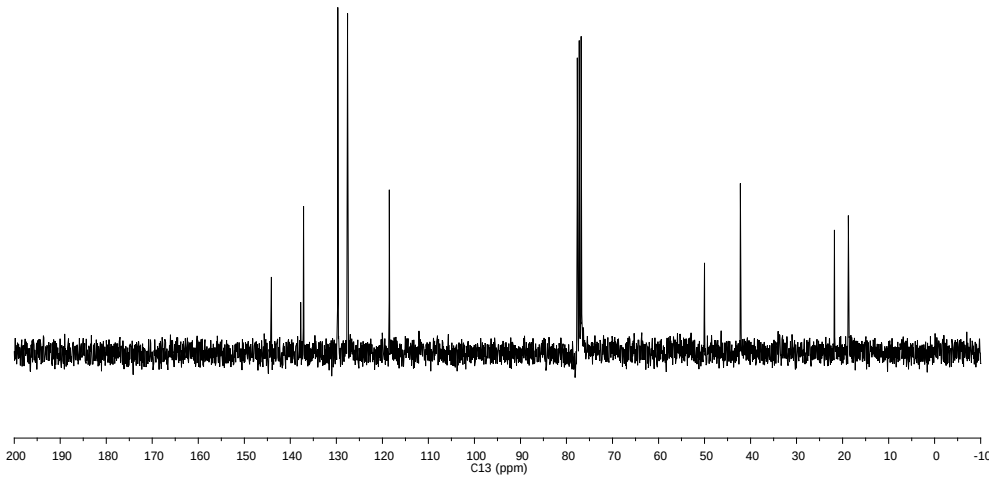
H1 (ppm)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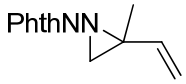
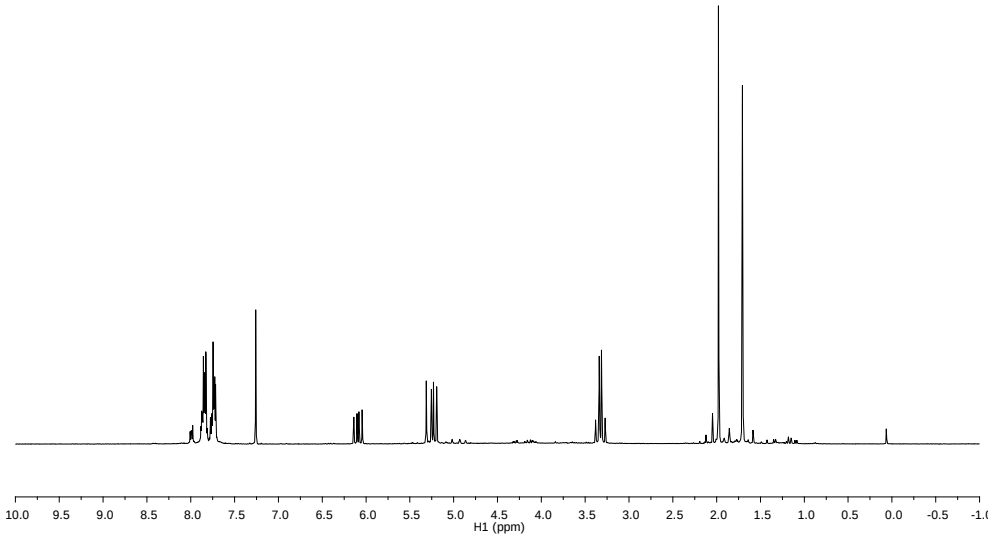
C13 (ppm)


PhthNN

2.3d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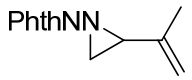
H1 (ppm)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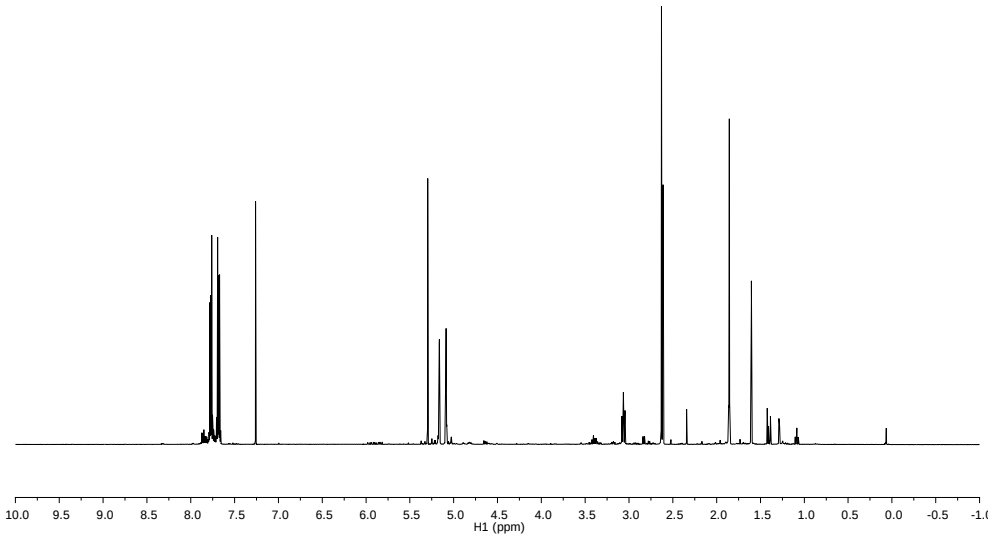
2.3e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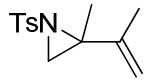
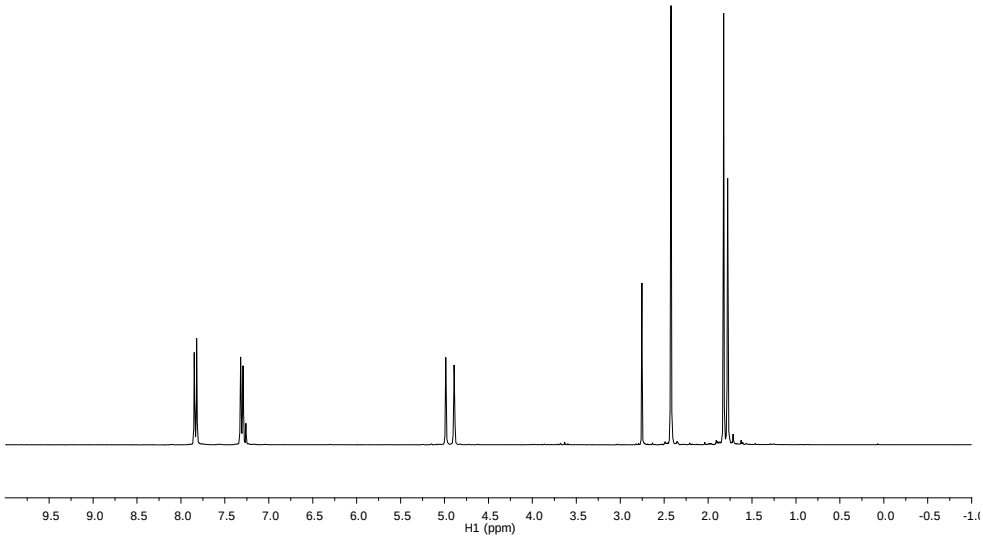
H1 (ppm)


TsN

2.3f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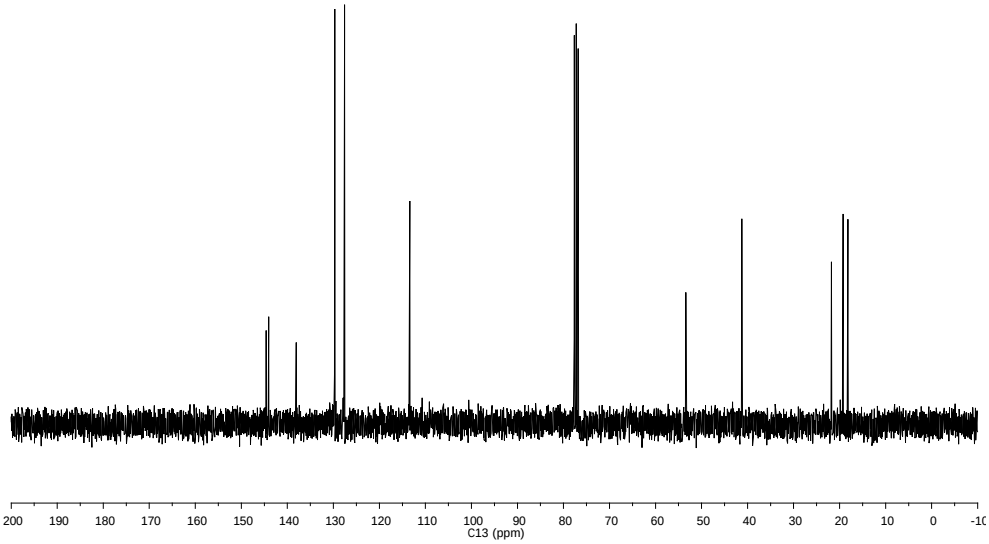
H1 (ppm)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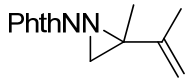
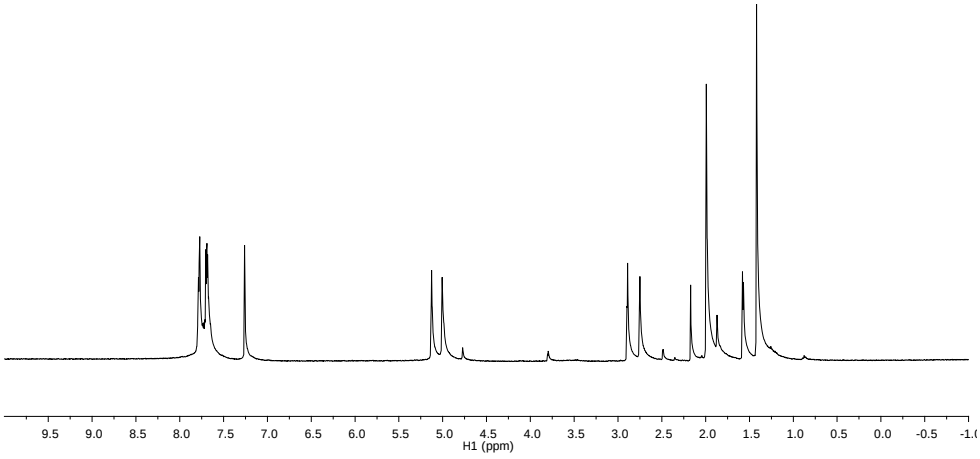

PhthNN

2.3g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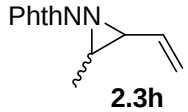
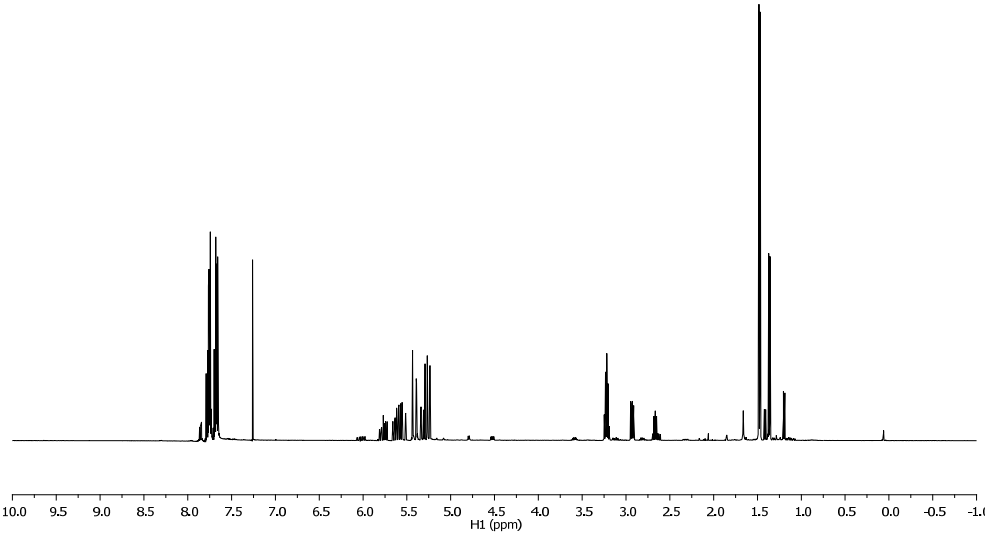
H1 (ppm)


PhthNN

2.3h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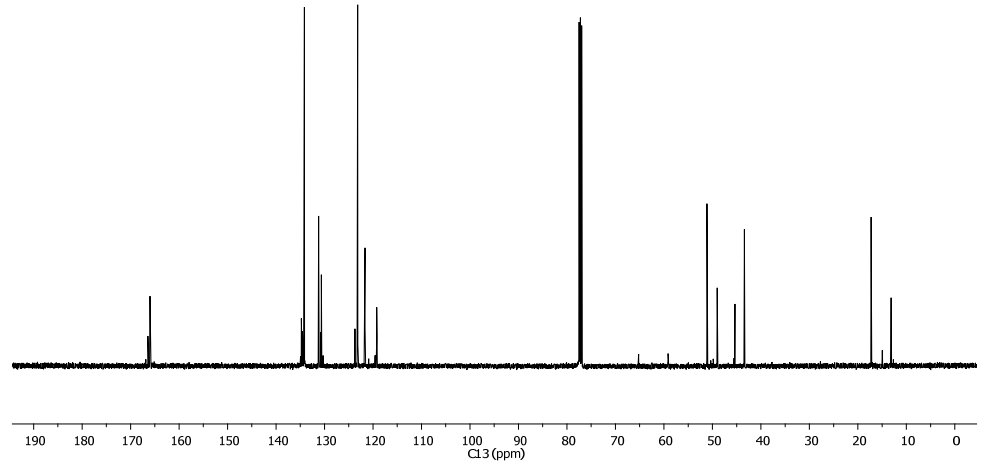
H1 (ppm)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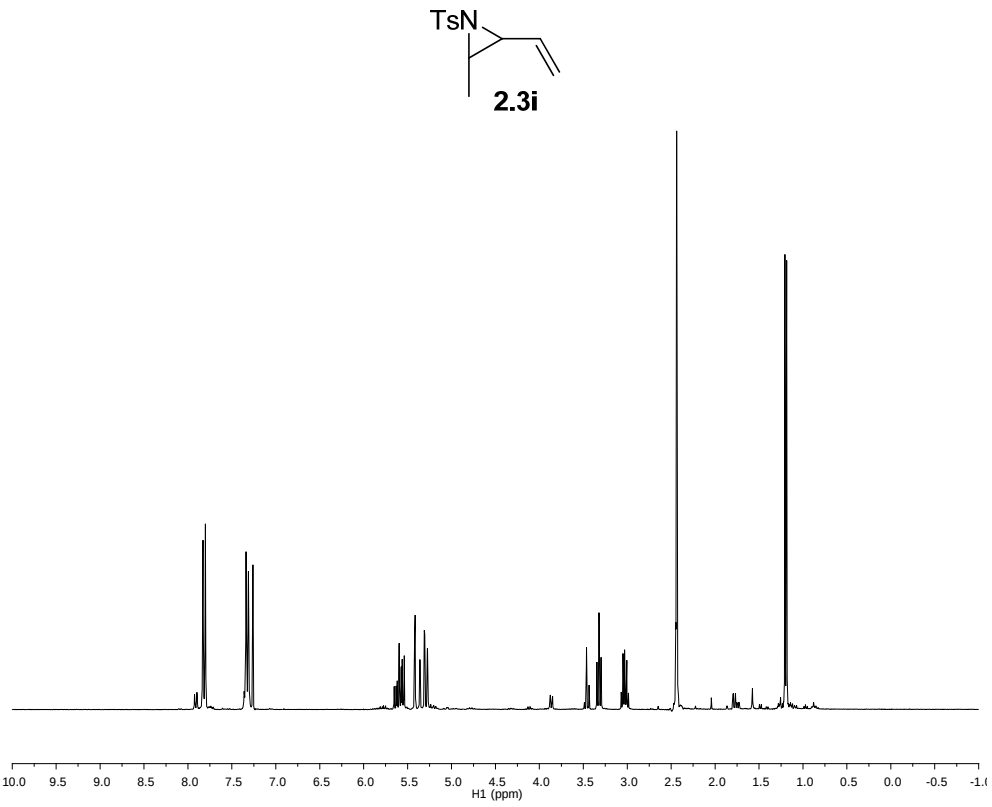
TsN
2.3i
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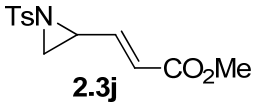
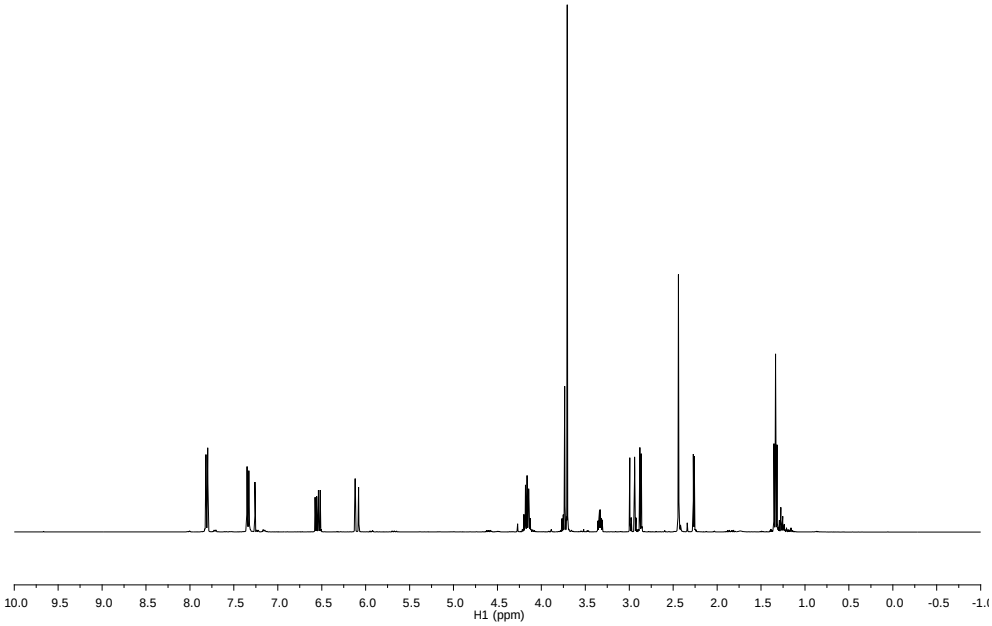
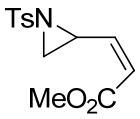
H1 (ppm)

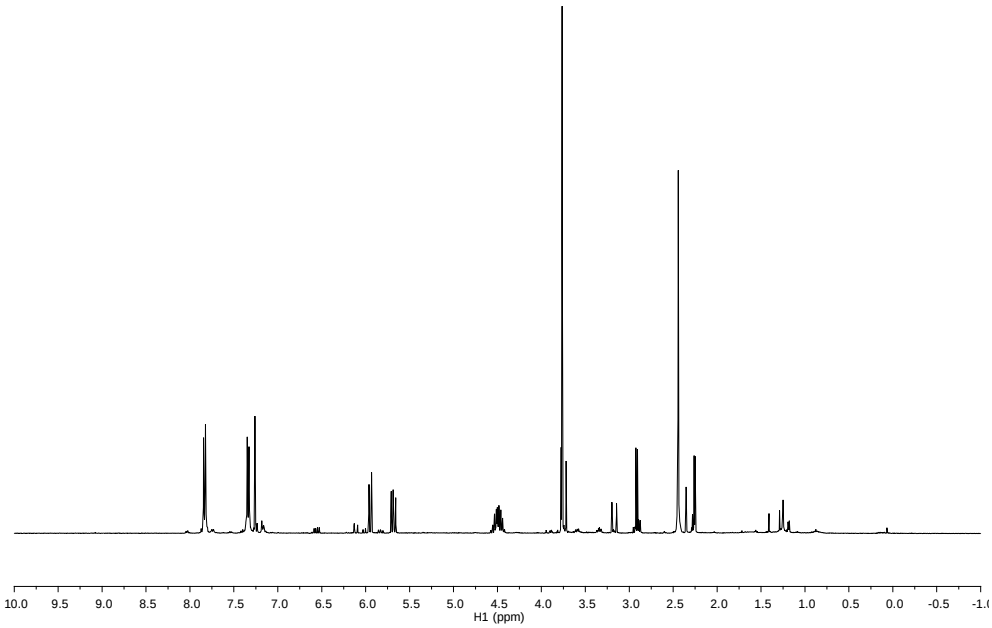

TsN
CO2Me

2.3j


10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
H1 (ppm)


TsN
MeO2C

2.3j *cis*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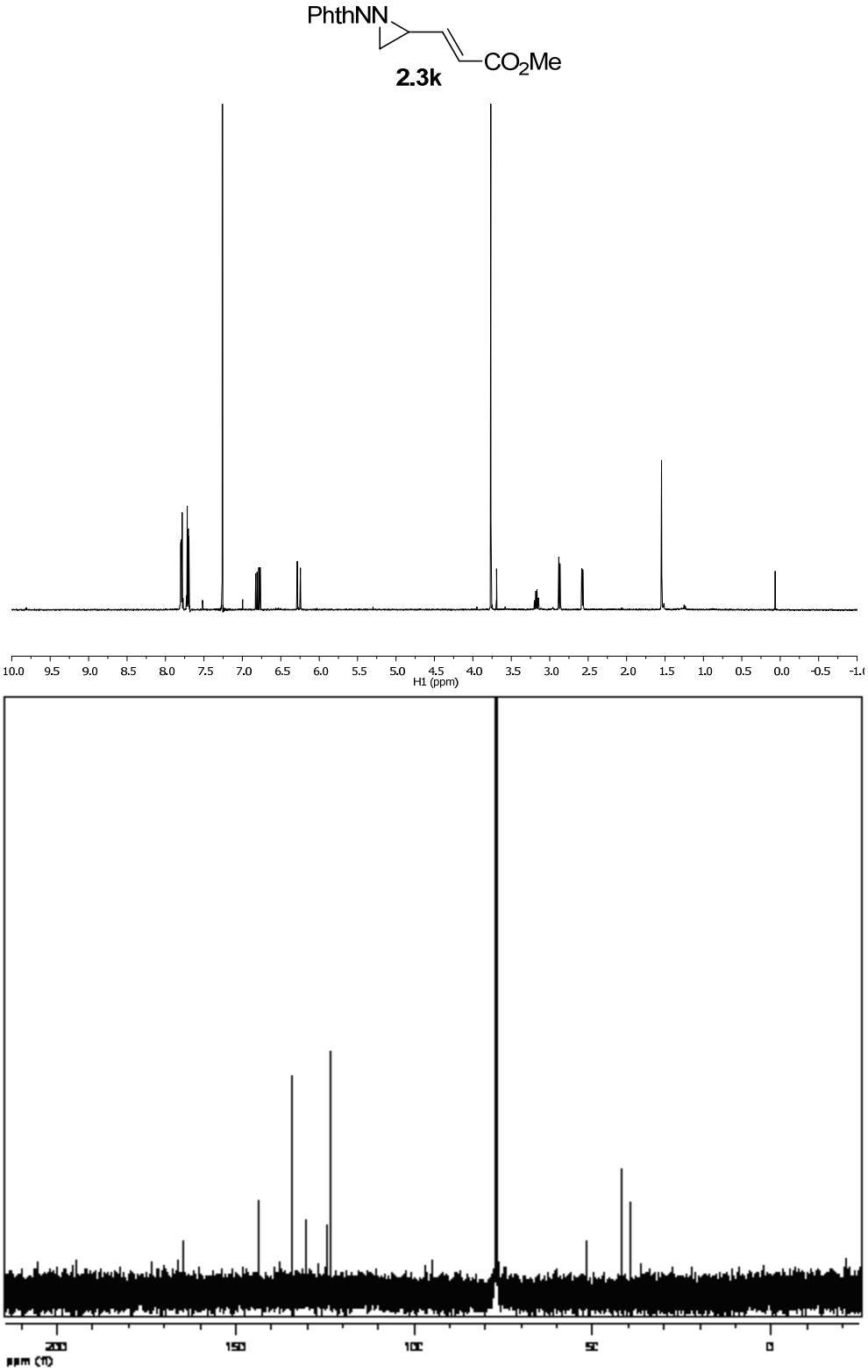
H1 (ppm)


PhthNN
CO2Me
2.3k
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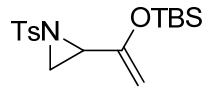
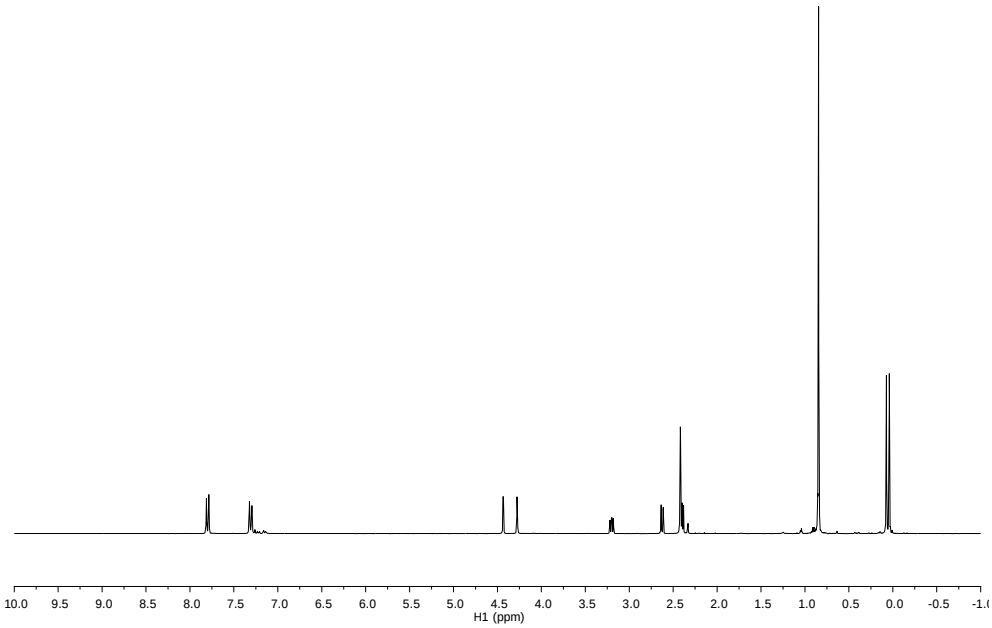
H1 (ppm)
200
150
100
50
0
ppm (f1)


TsN
OTBS

2.3l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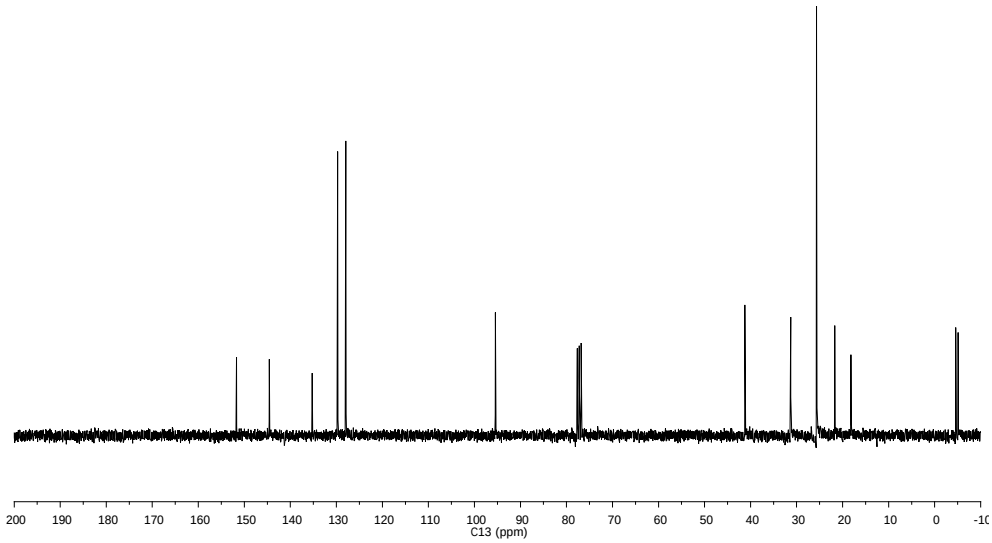
H1 (ppm)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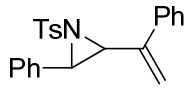
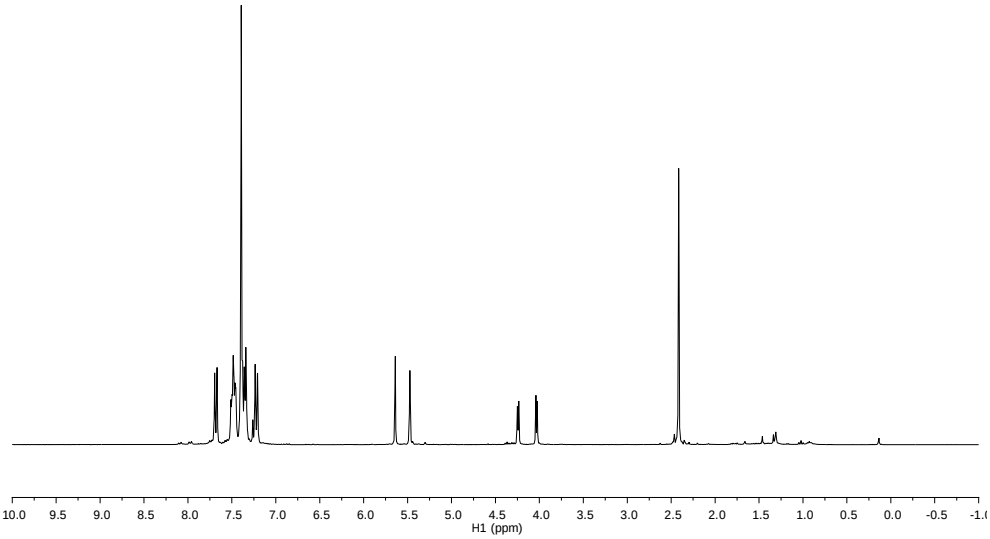
C13 (ppm)


TsN
Ph
Ph

2.3m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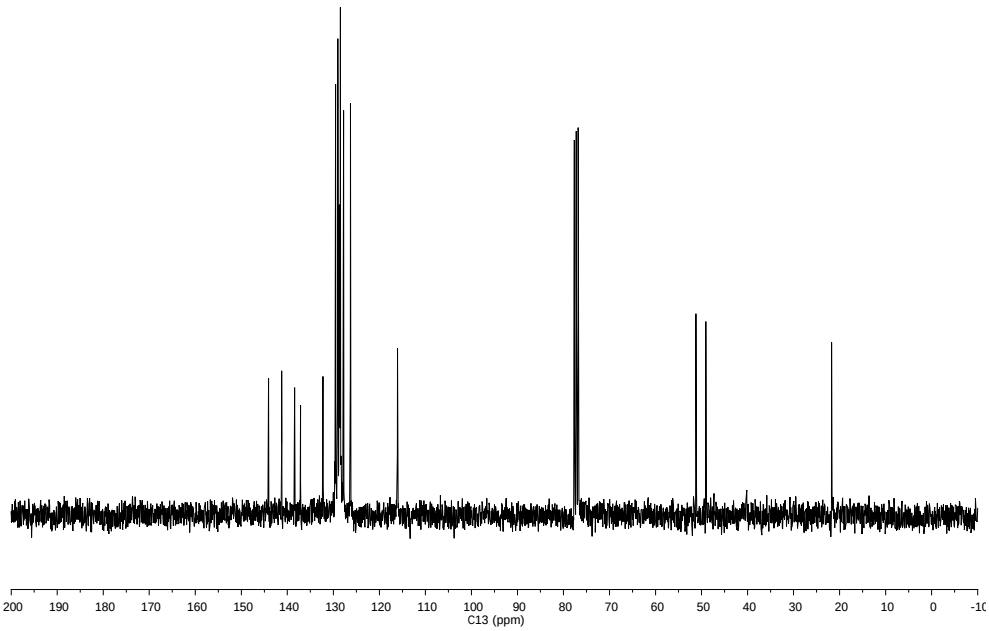
H1 (ppm)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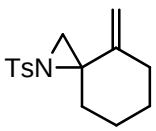
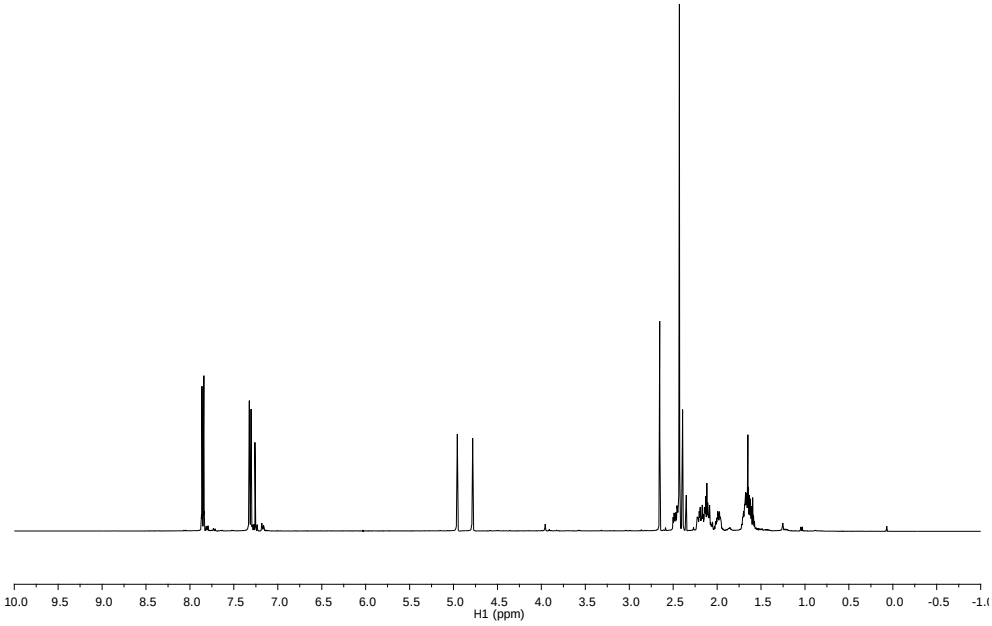
C13 (ppm)


TsN

2.3n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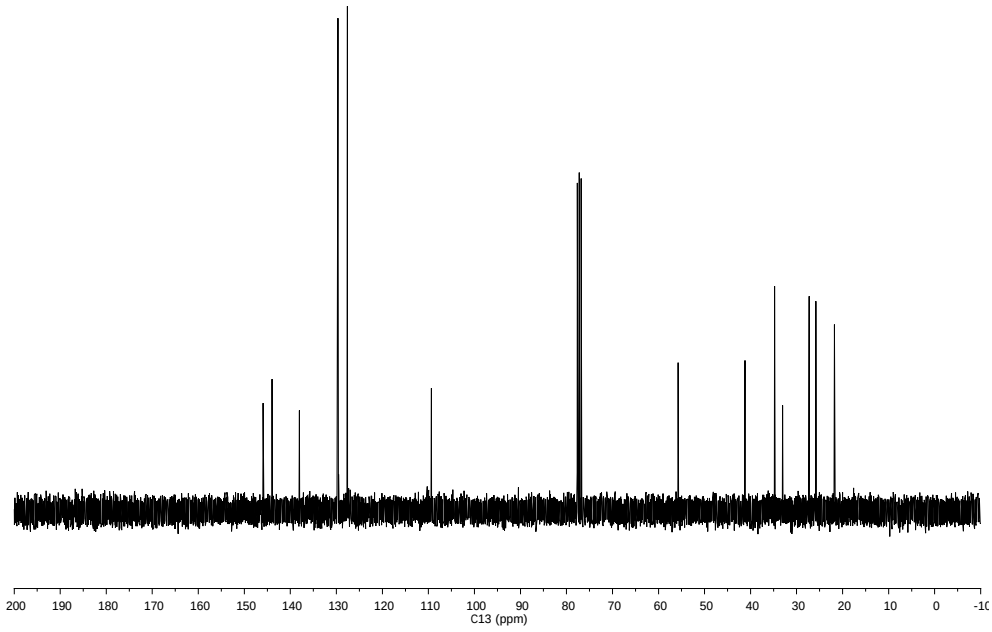
H1 (ppm)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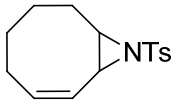
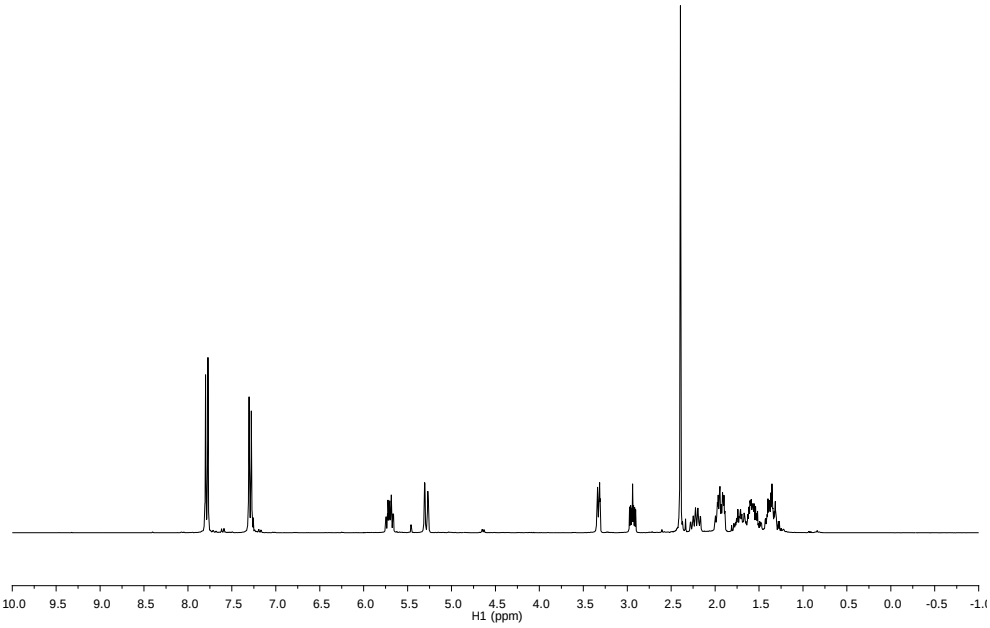
C13 (ppm)


NTs

2.3o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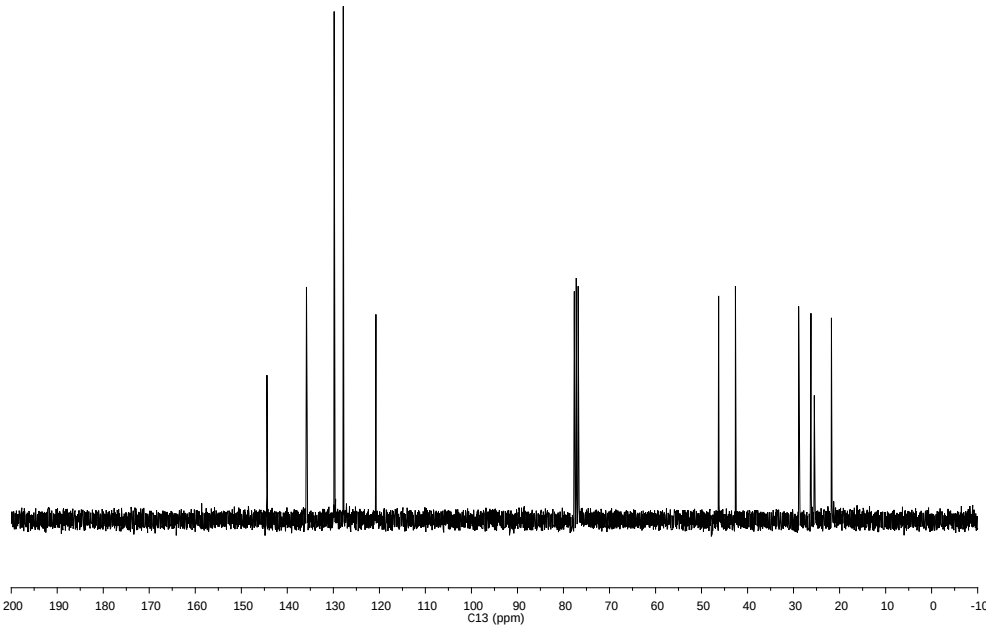
H1 (ppm)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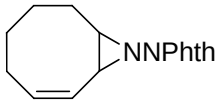
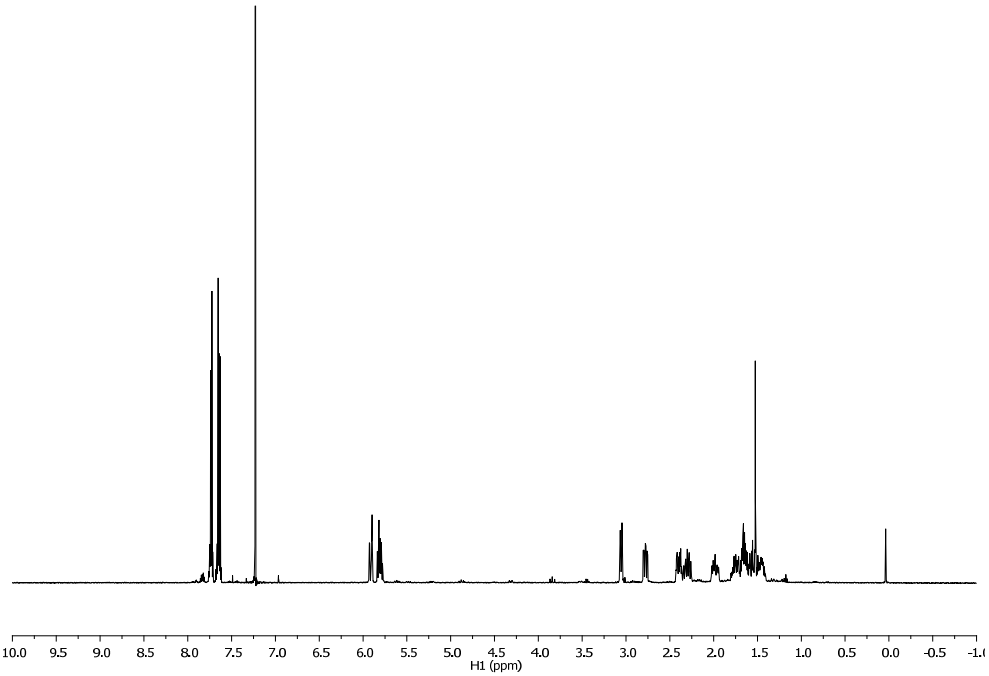
C13 (ppm)


NNPhth

2.3p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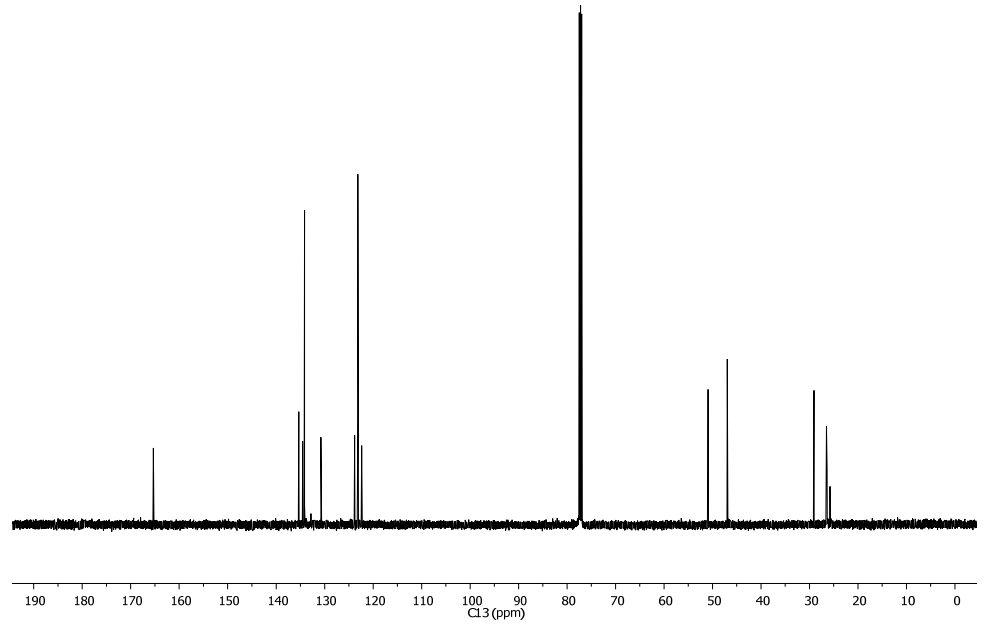
H1 (ppm)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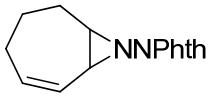
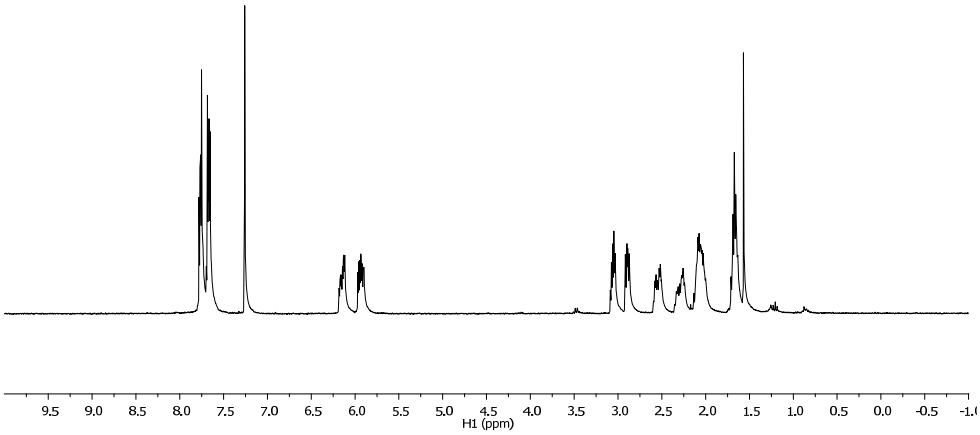
C13 (ppm)


NNPhth

2.3q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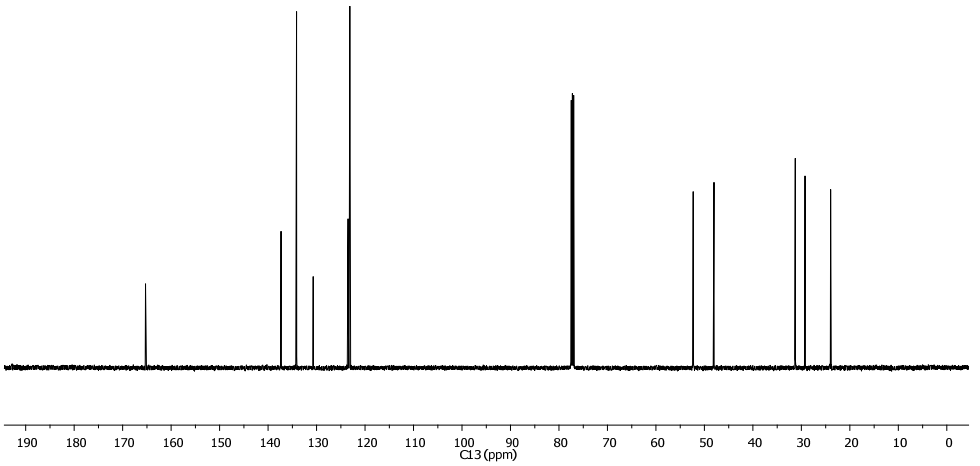
H1 (ppm)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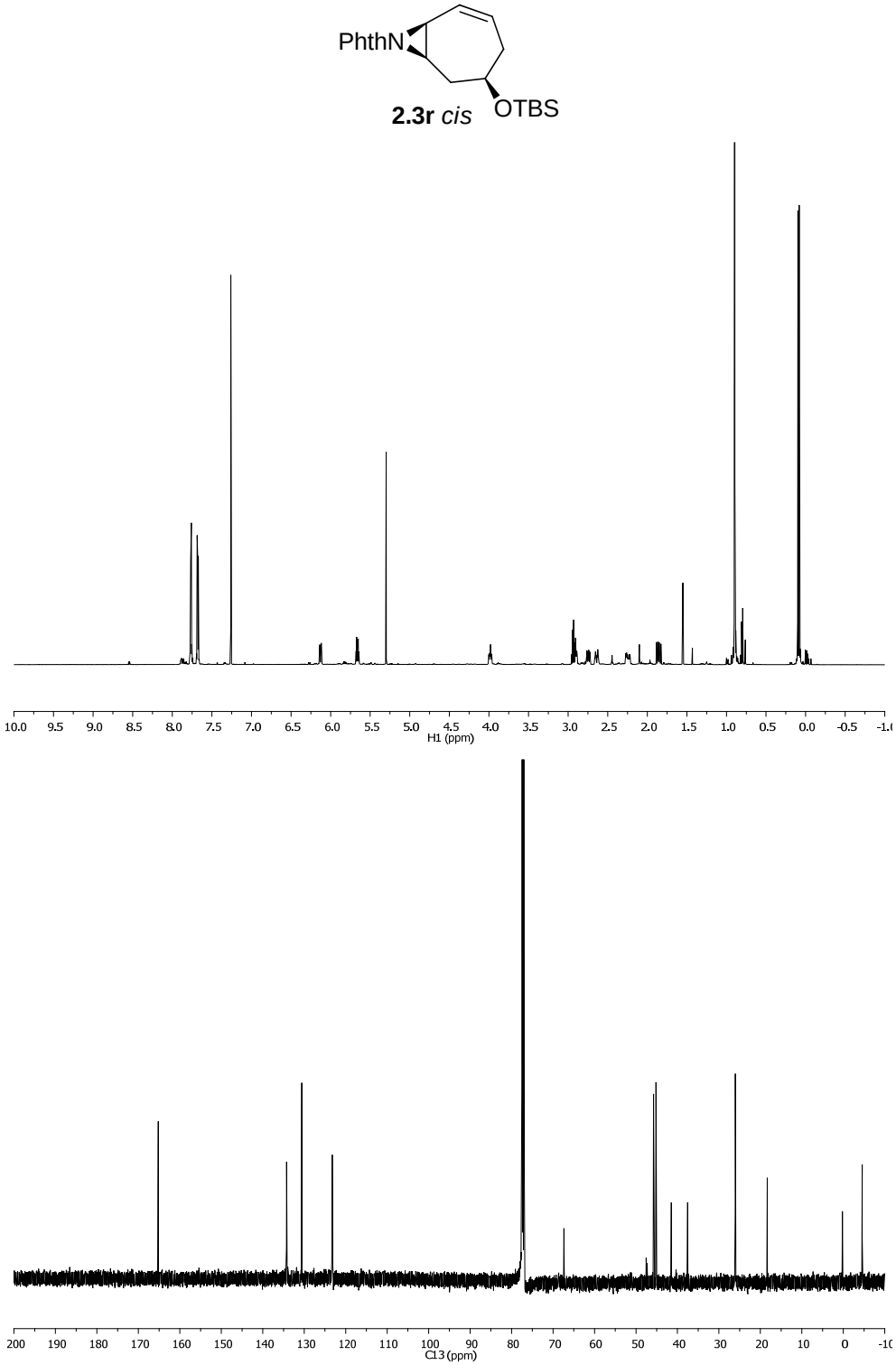
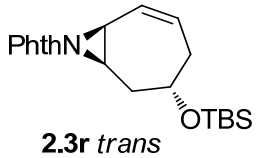
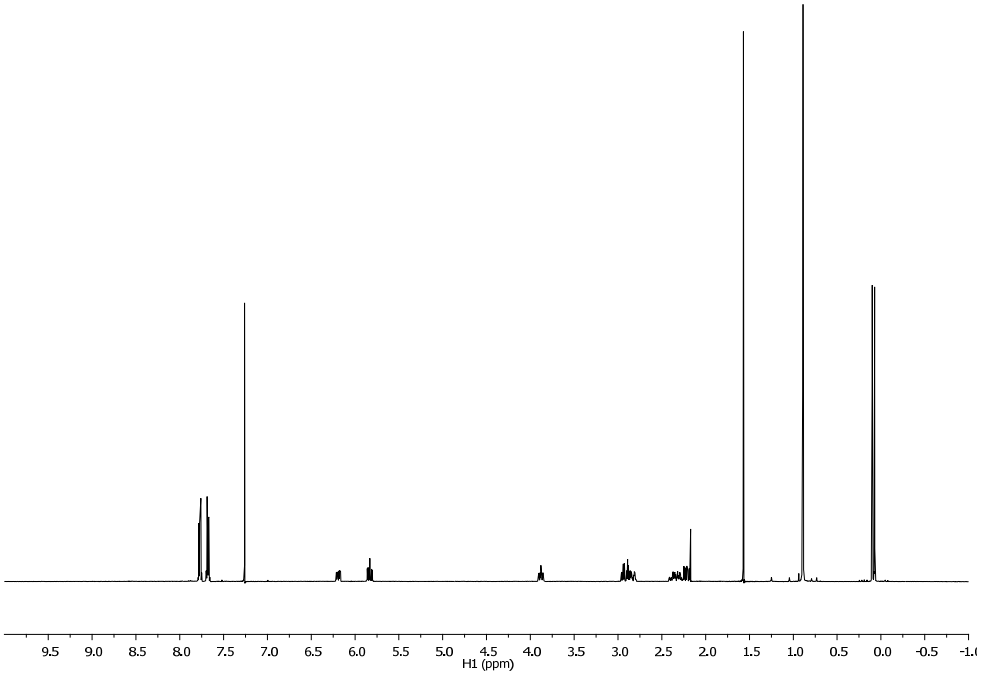
C13 (ppm)



2.3r *cis*


PhthN
OTBS

2.3r *trans*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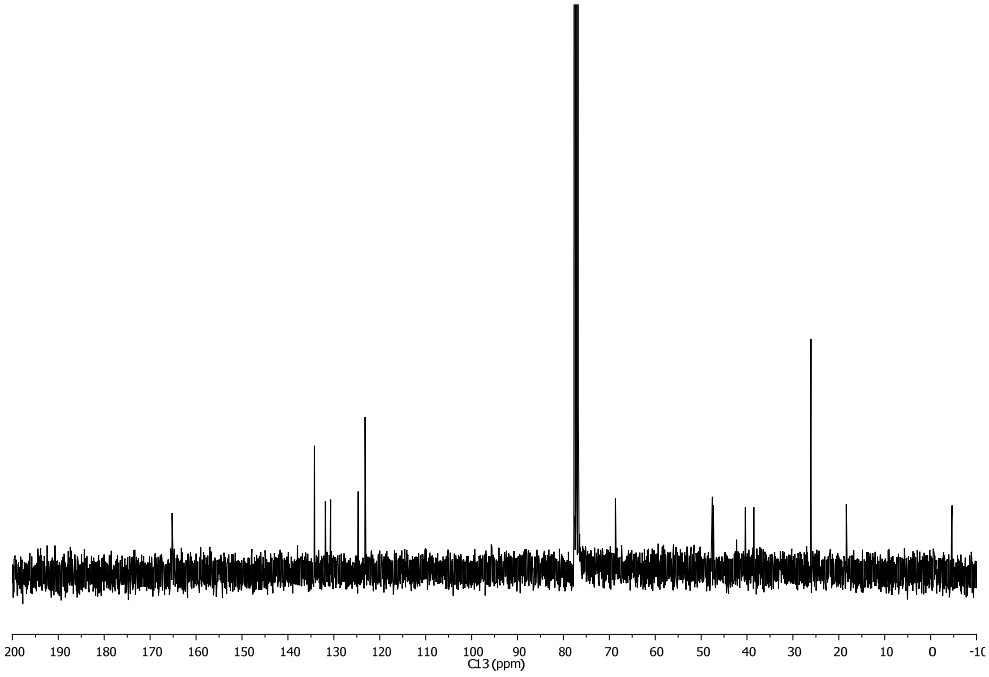
H1 (ppm)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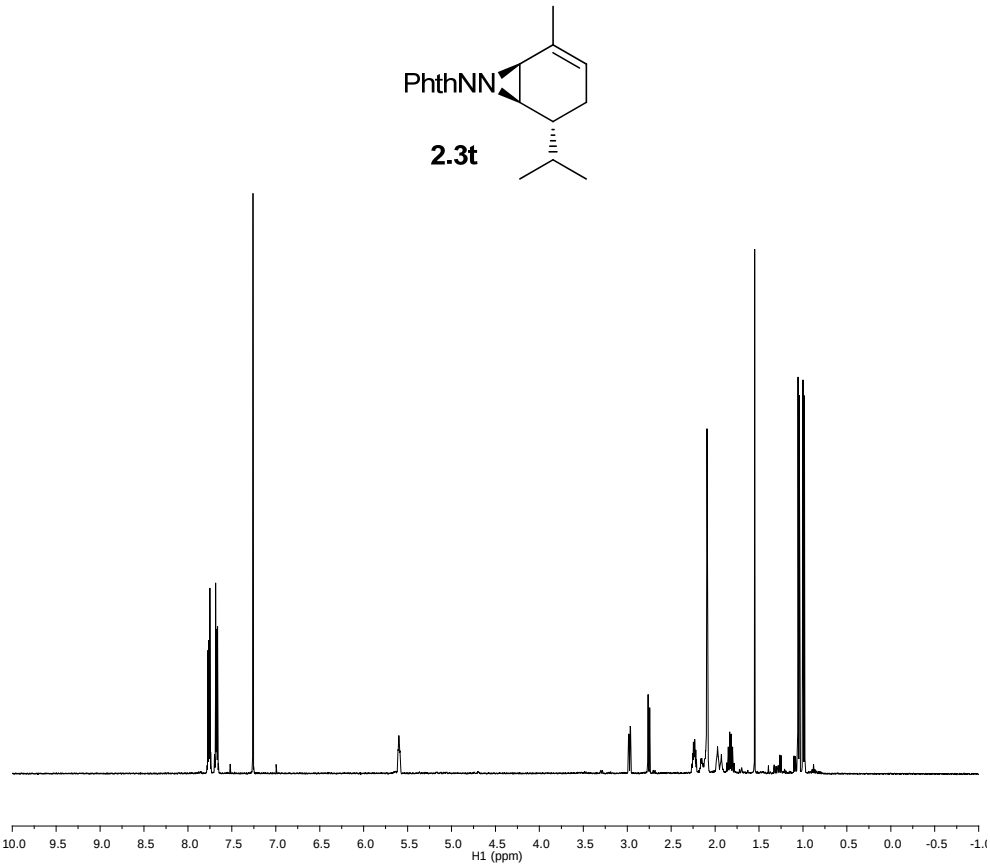
C13 (ppm)


PhthNN
2.3t
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
H1 (ppm)
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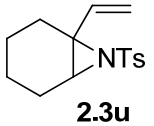
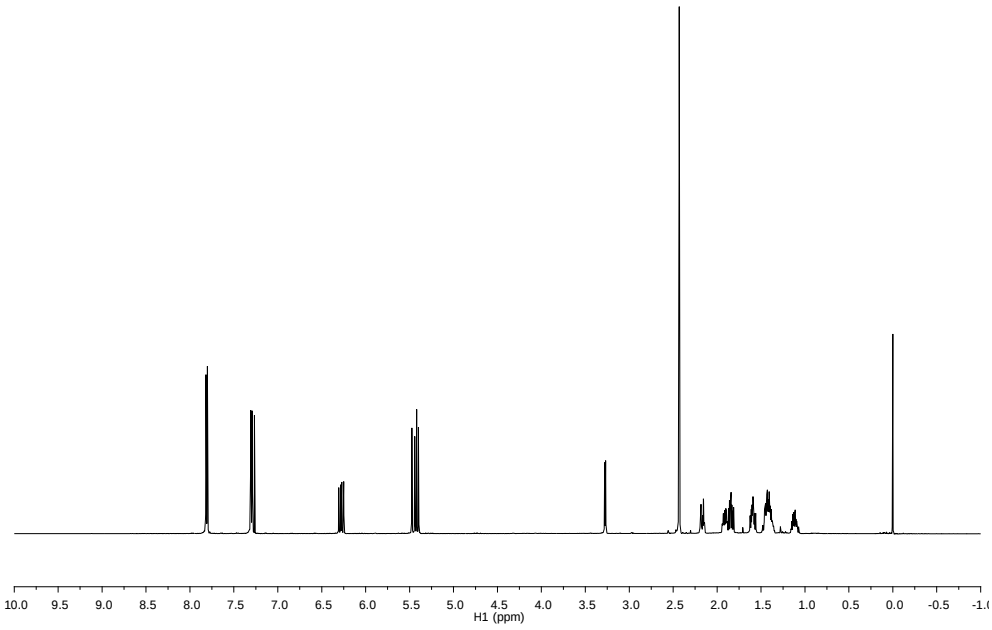
C13 (ppm)


NTs

2.3u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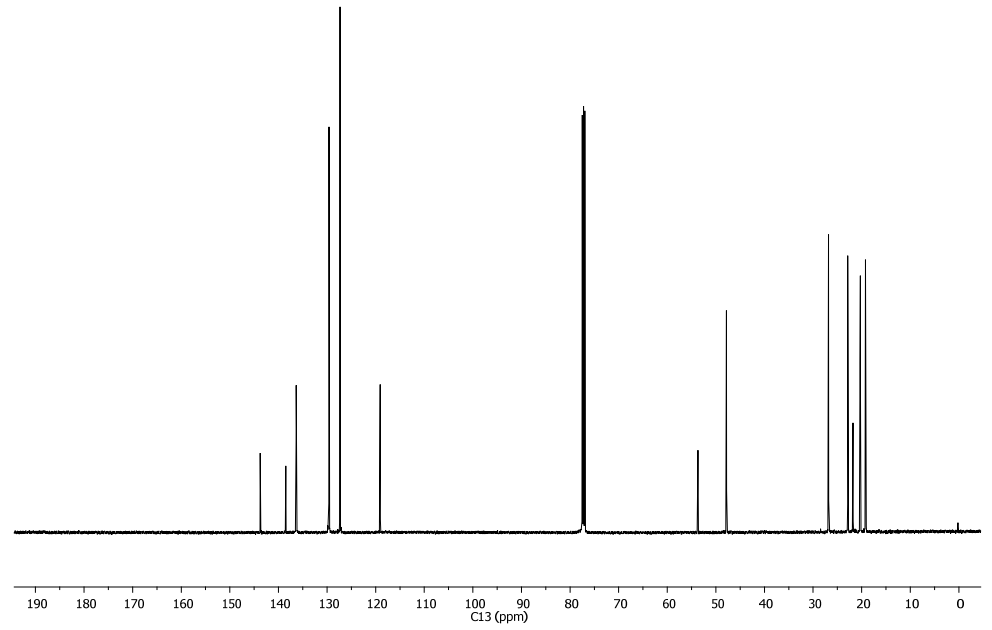
H1 (ppm)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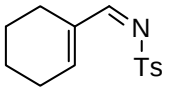
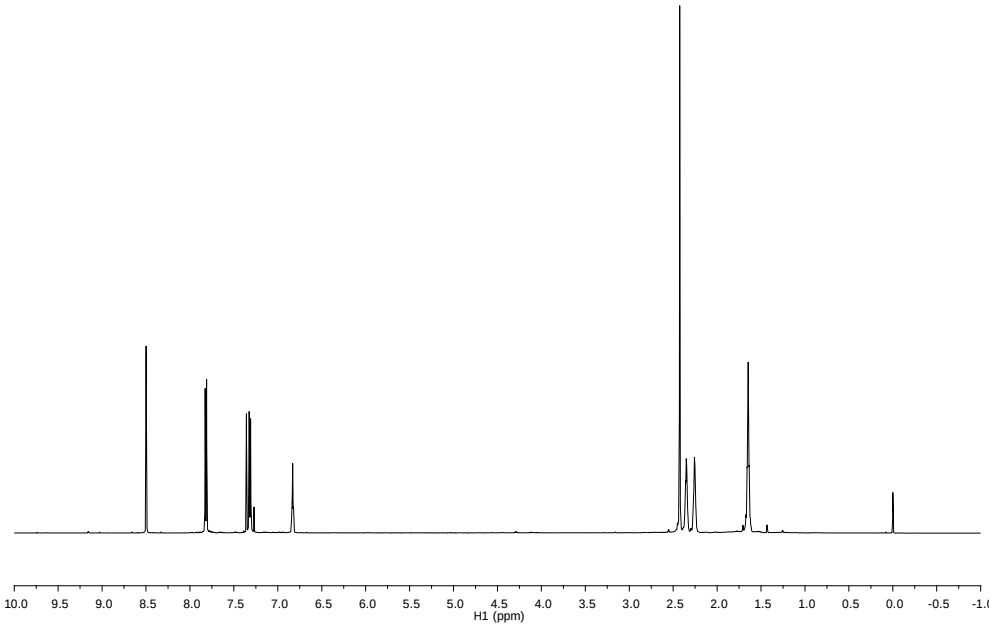
C13 (ppm)


N
Ts

2.26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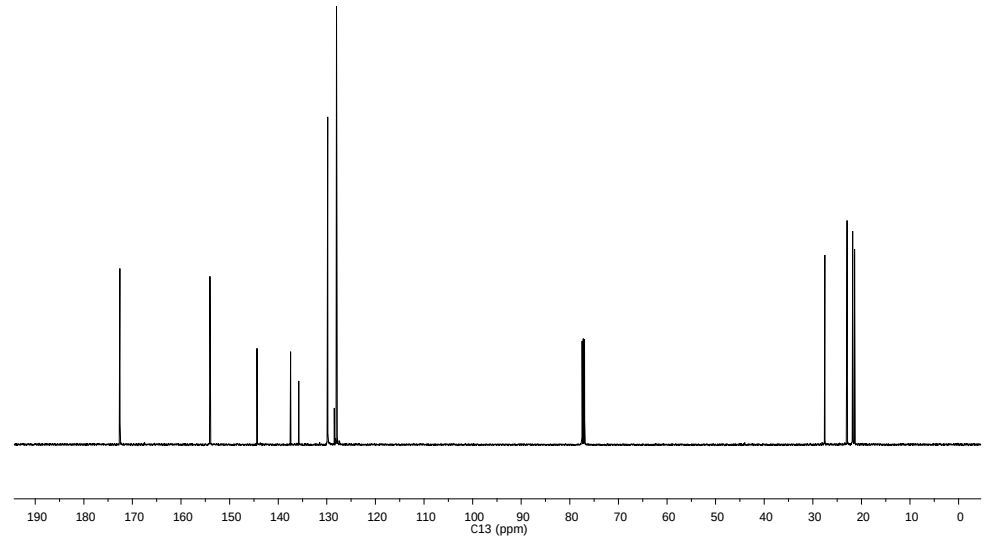
H1 (ppm)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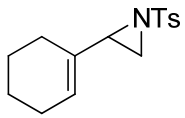
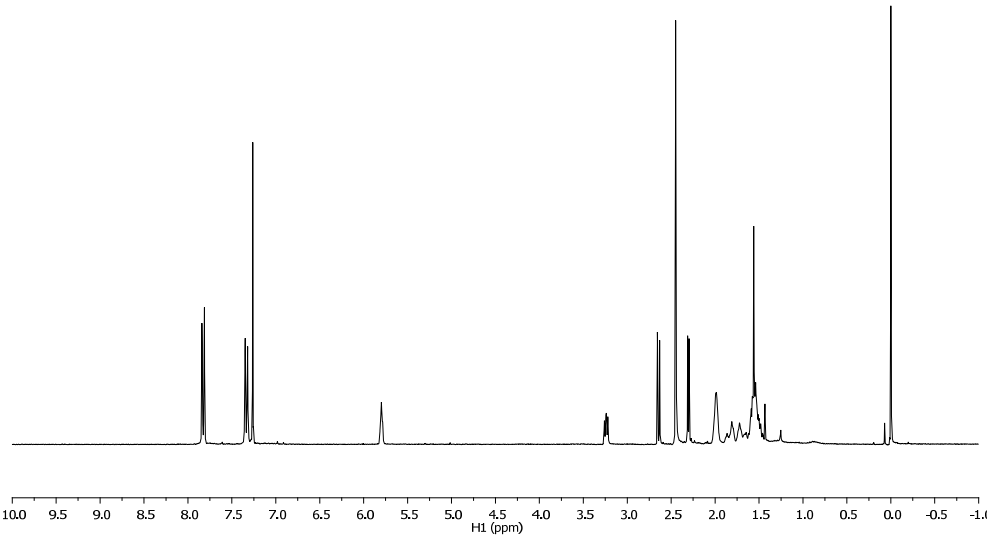
C13 (ppm)


NTs

2.3v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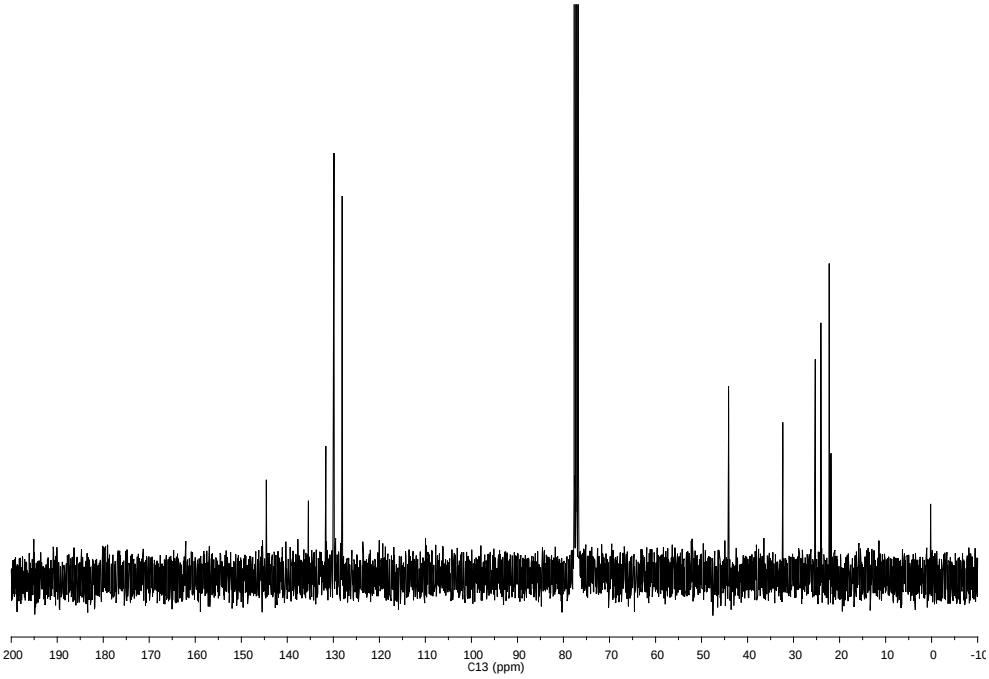
H1 (ppm)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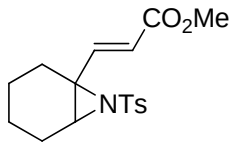
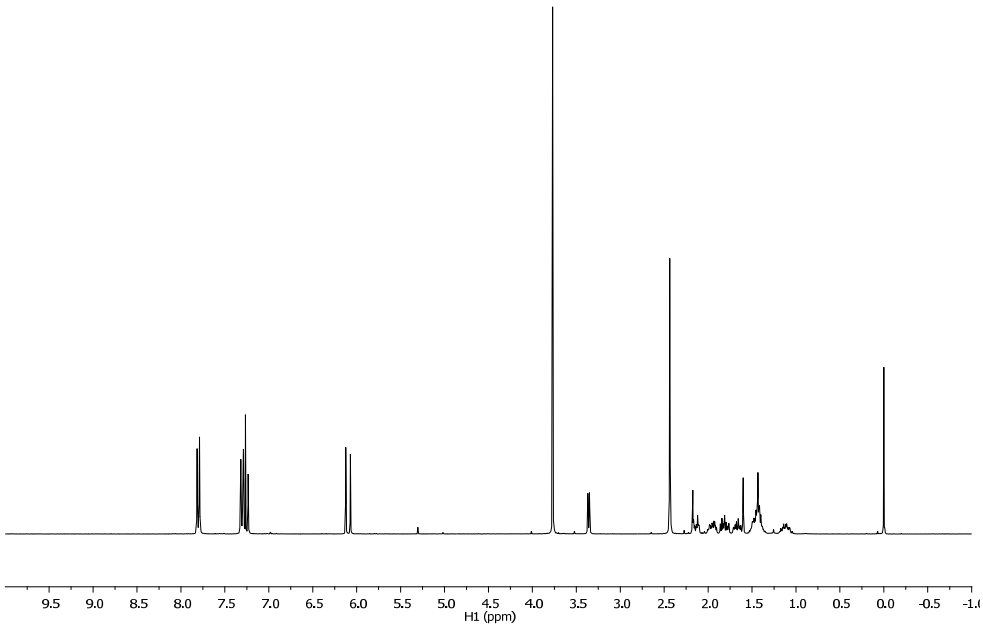
C13 (ppm)


CO2Me
NTs

2.3w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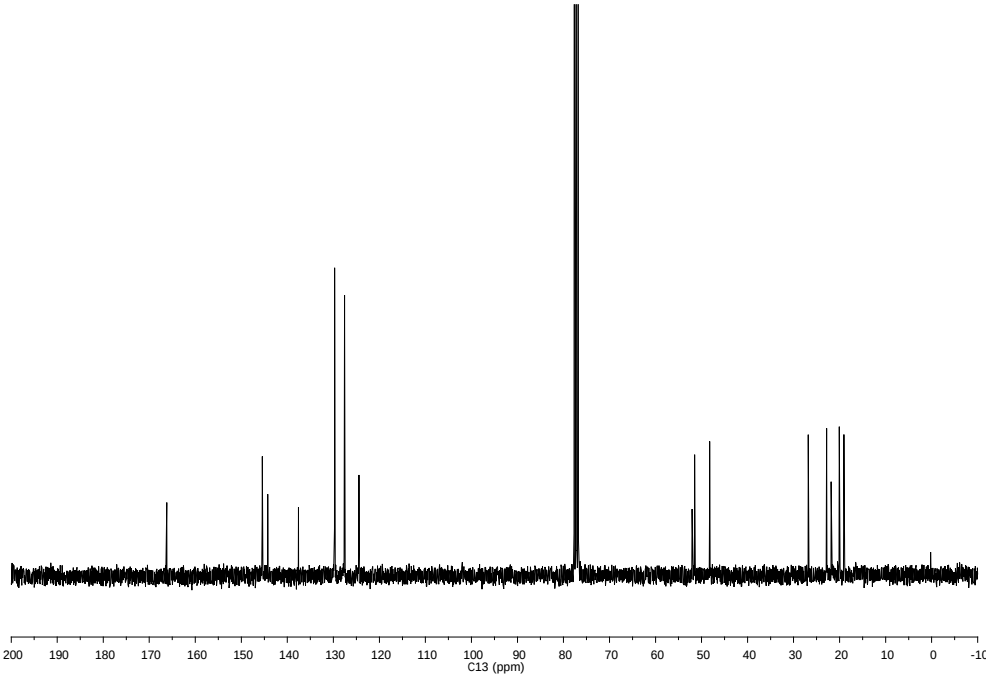
H1 (ppm)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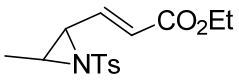
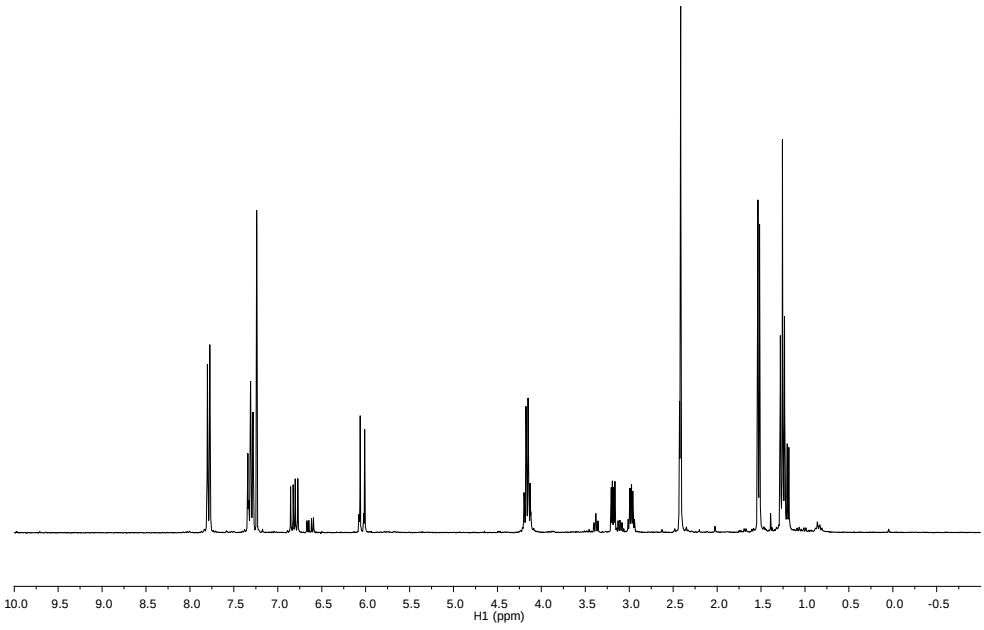
C13 (ppm)


CO2Et
NTs

2.3x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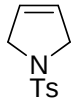
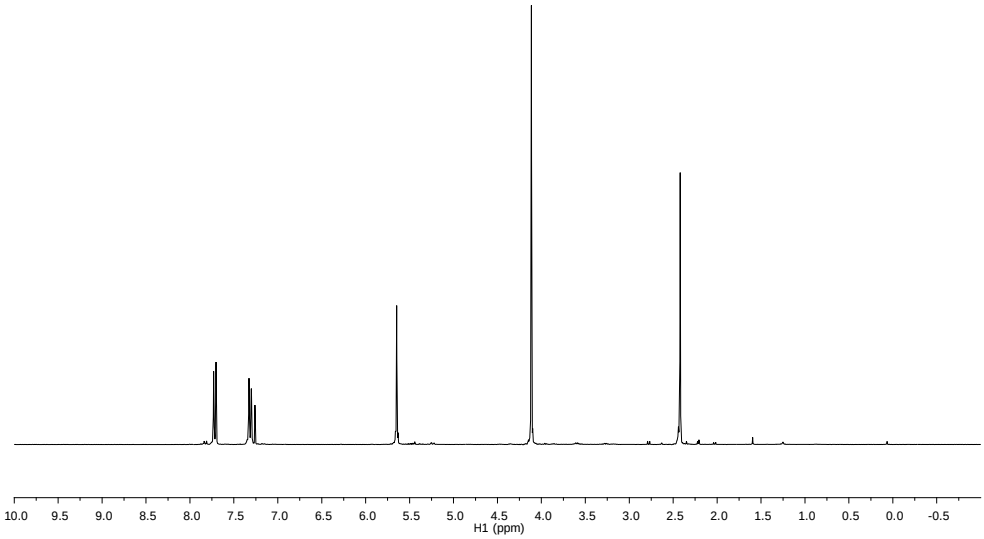
H1 (ppm)


N
Ts

2.4a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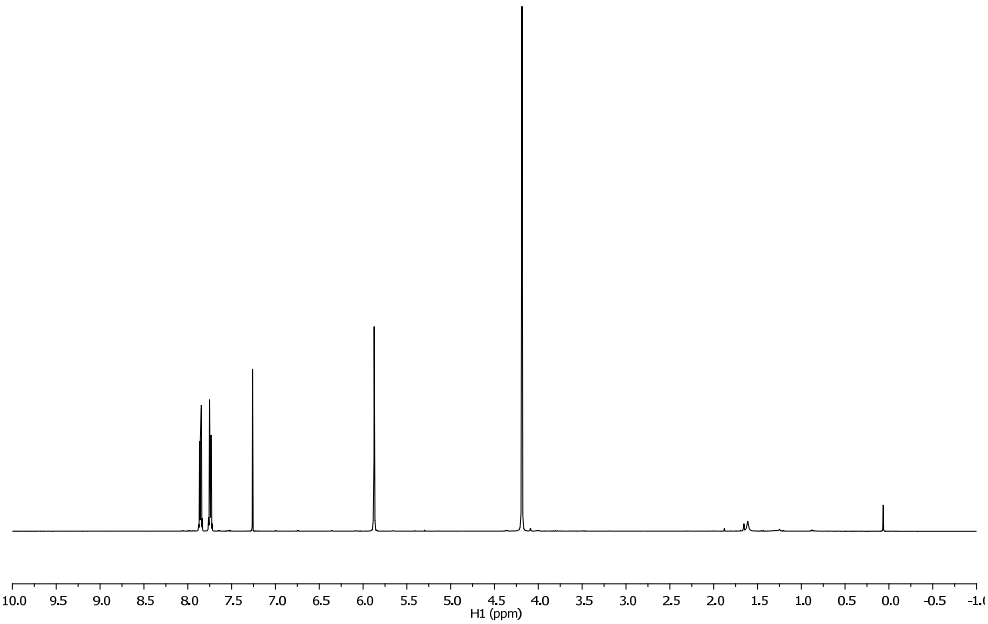
H1 (ppm)


N
NPhth

2.4b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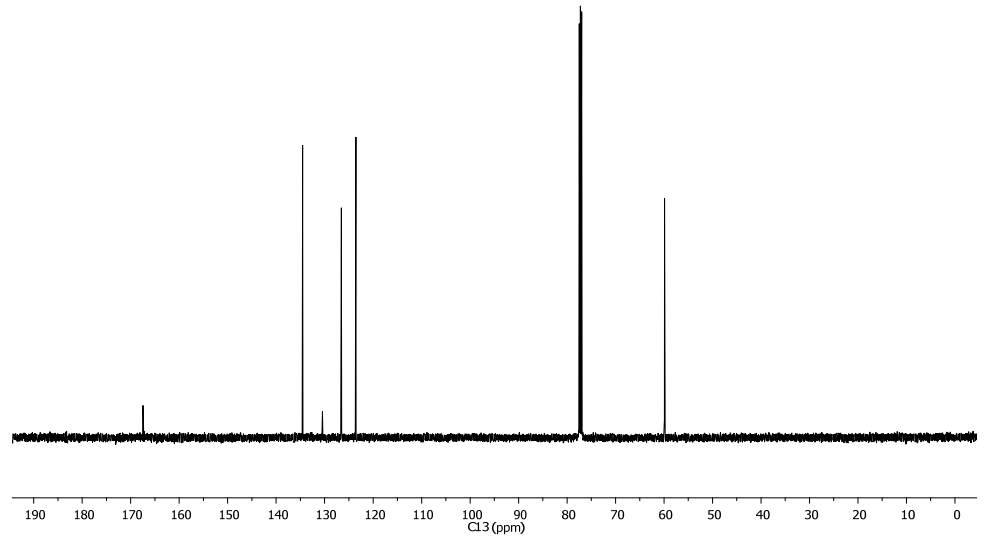
H1 (ppm)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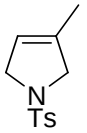
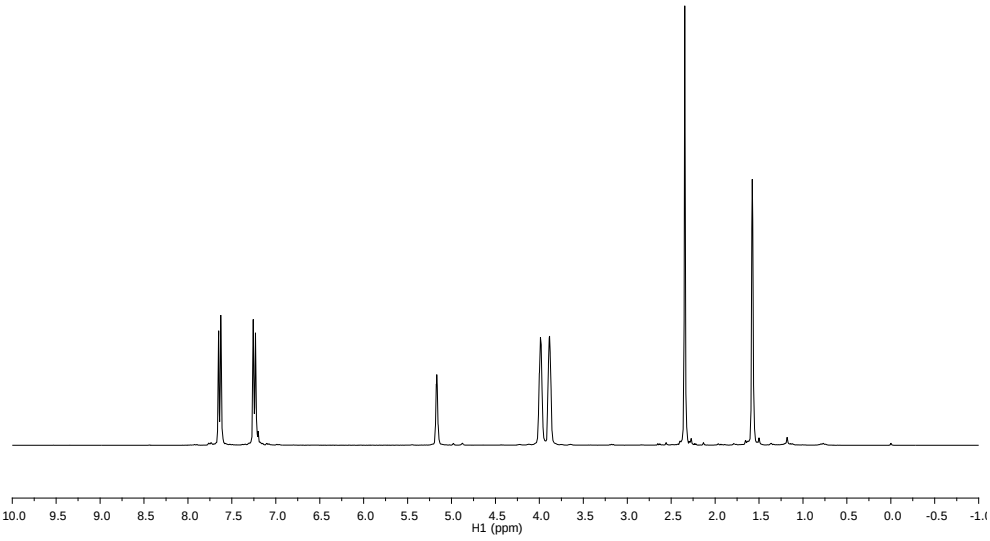
C13 (ppm)


N
Ts

2.4c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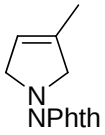
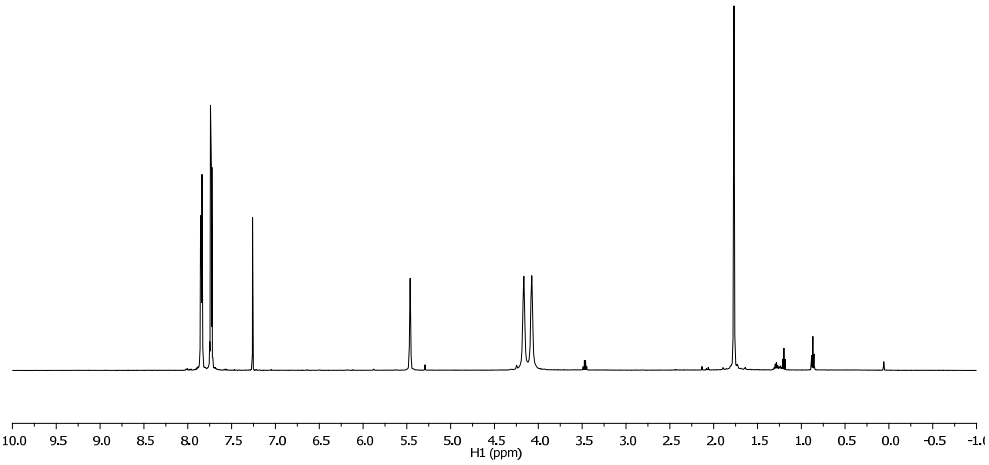
H1 (ppm)


N
NPhth

2.4d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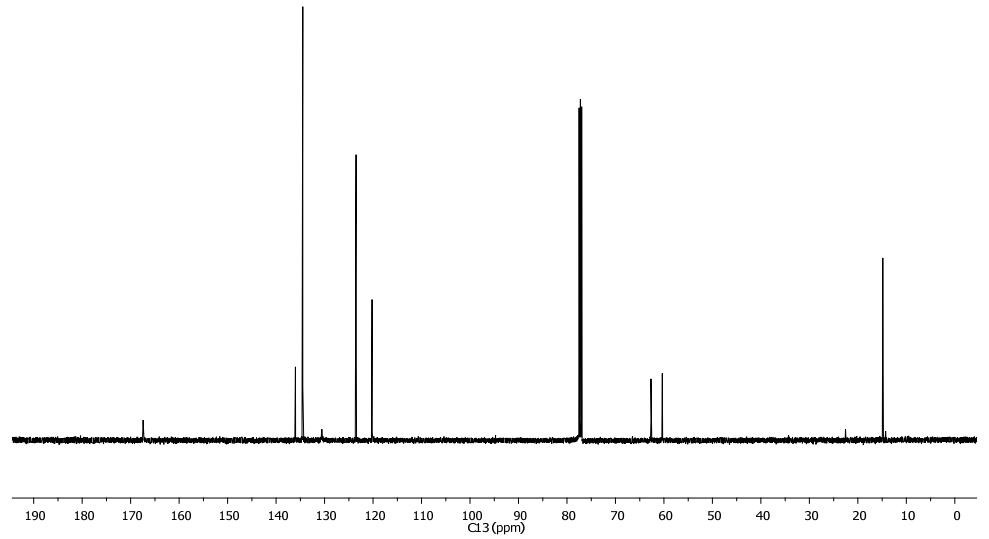
H1 (ppm)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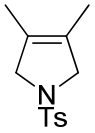
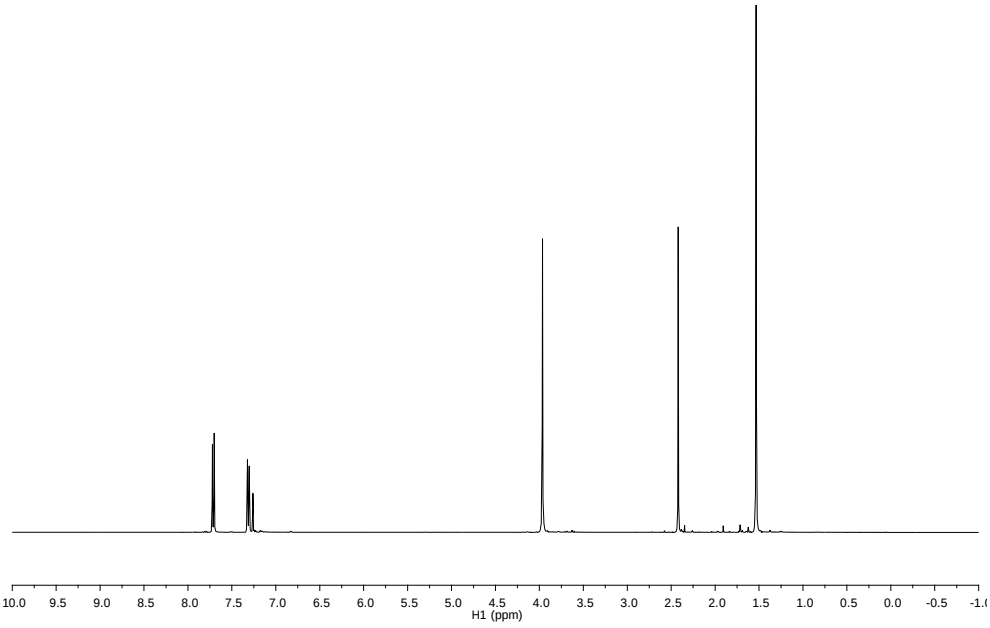
C13 (ppm)


N
Ts

2.4f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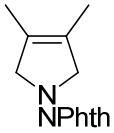
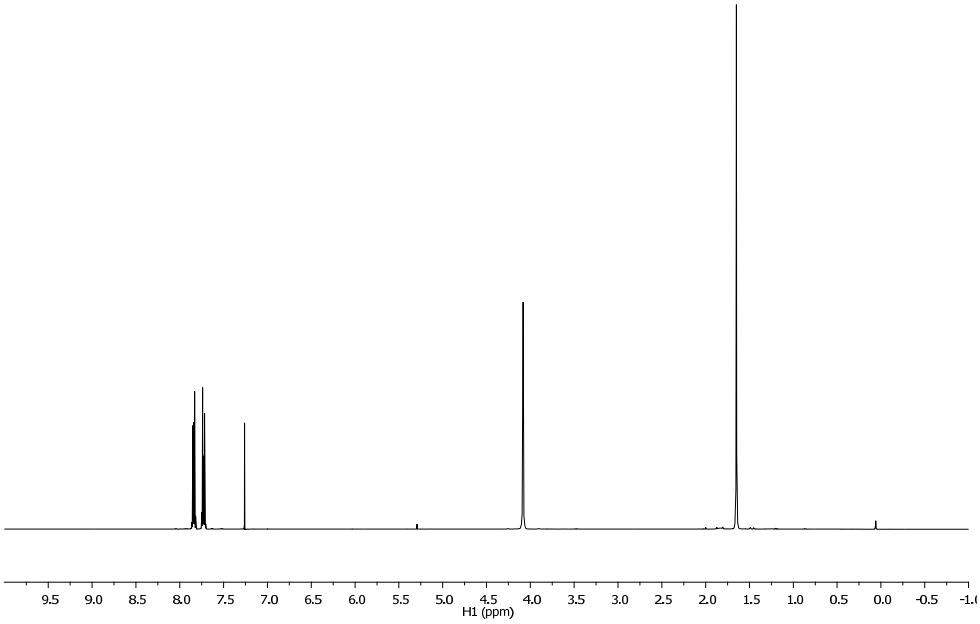
H1 (ppm)


N
NPhth

2.4g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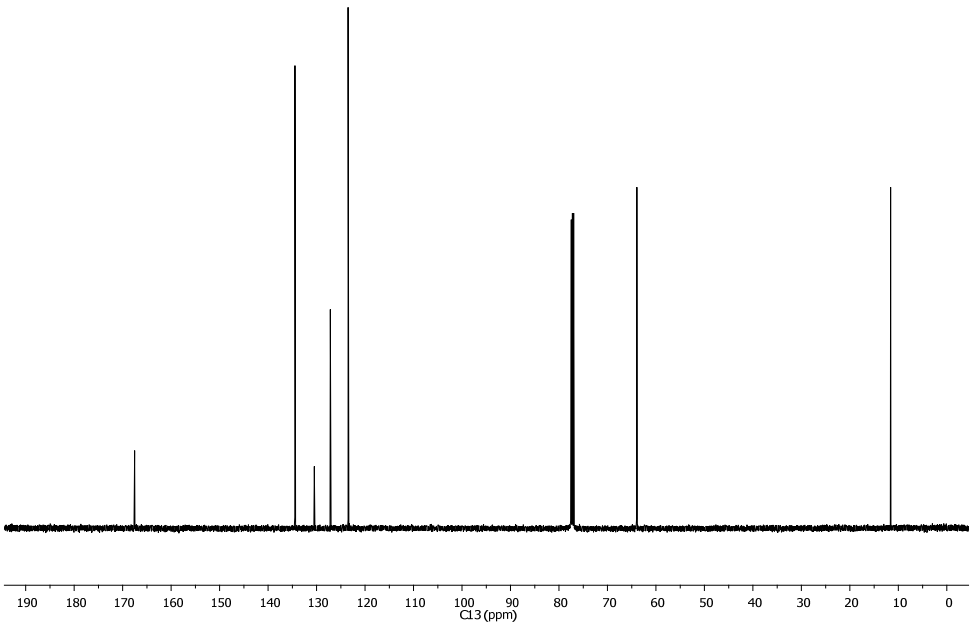
H1 (ppm)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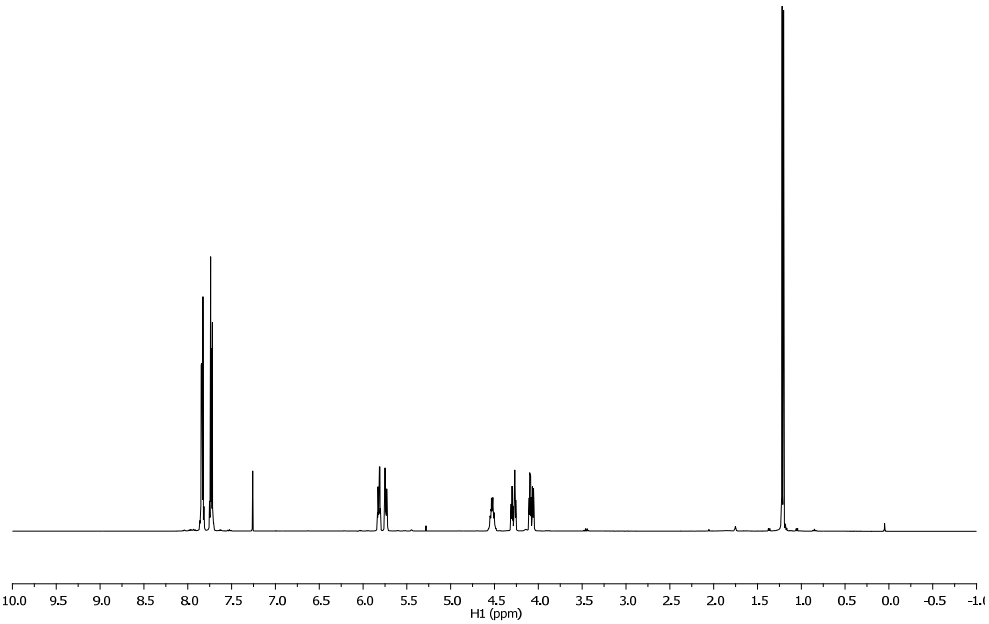
C13 (ppm)


N
NPhth

2.4h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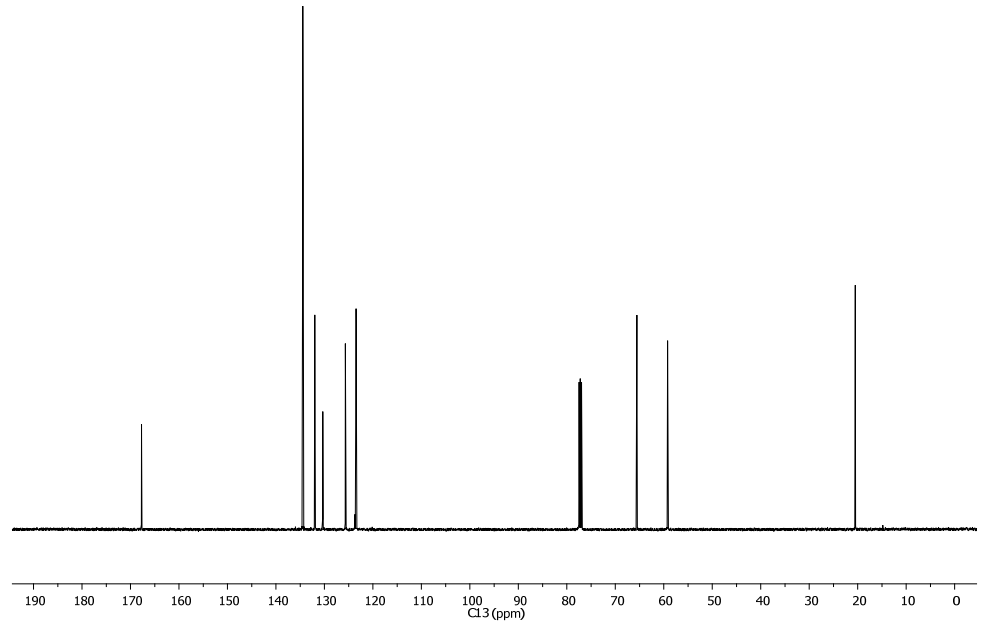
H1 (ppm)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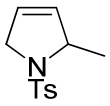
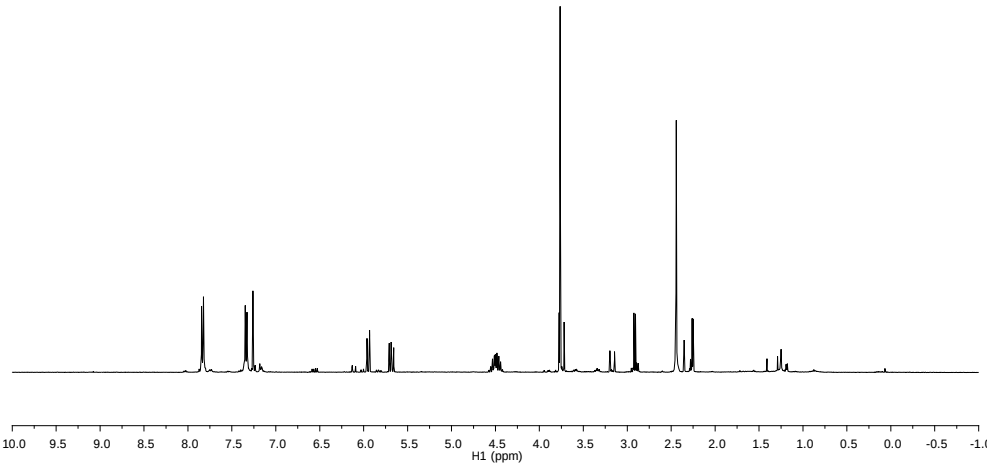
C13 (ppm)


N
Ts

2.4i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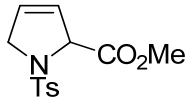
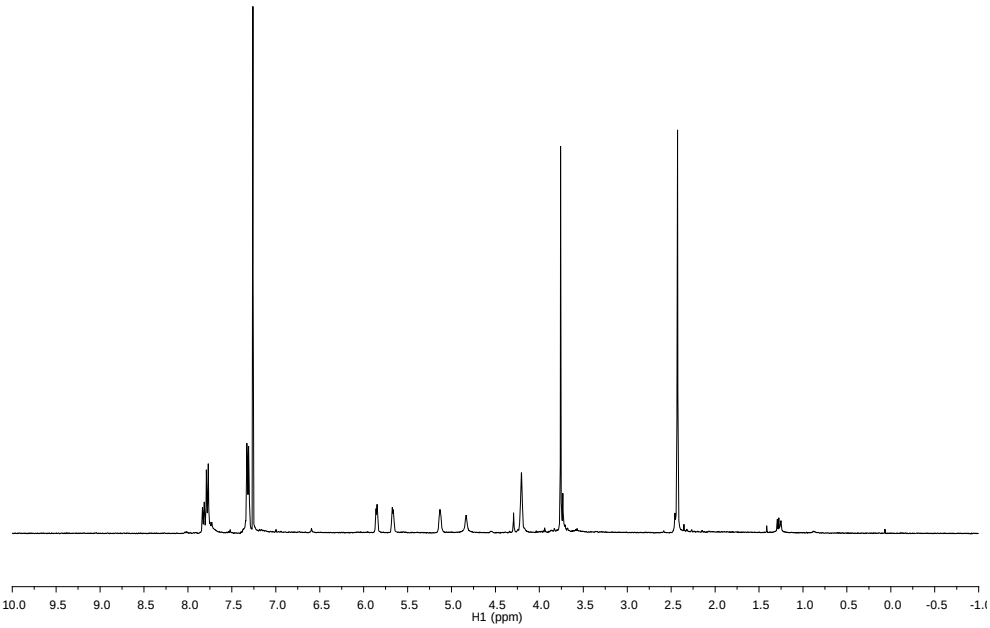
H1 (ppm)


CO2Me
N
Ts

2.4j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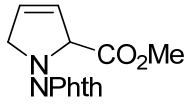
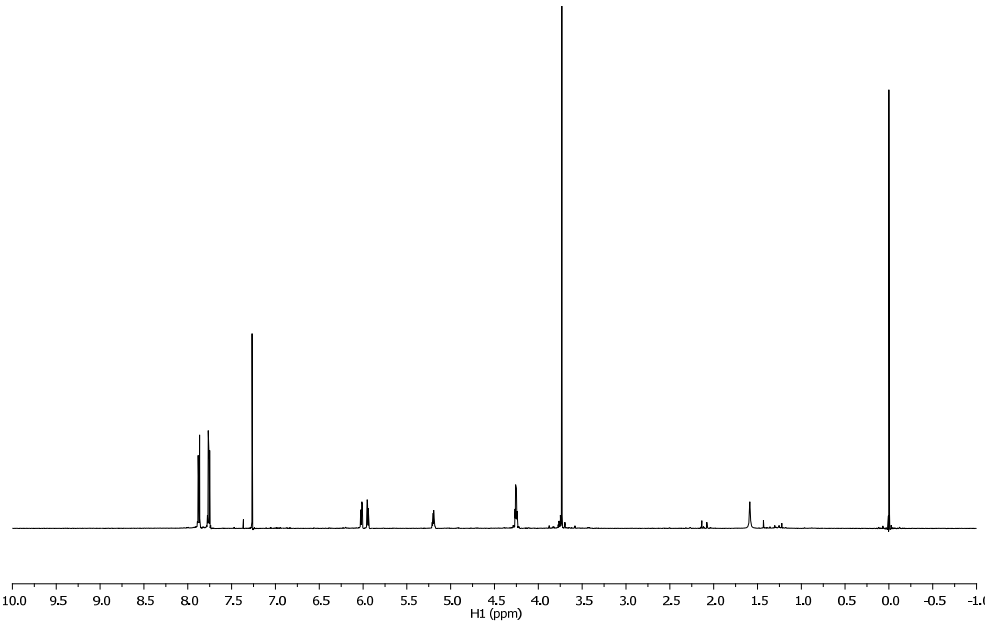
H1 (ppm)


CO2Me
N
NPhth

2.4k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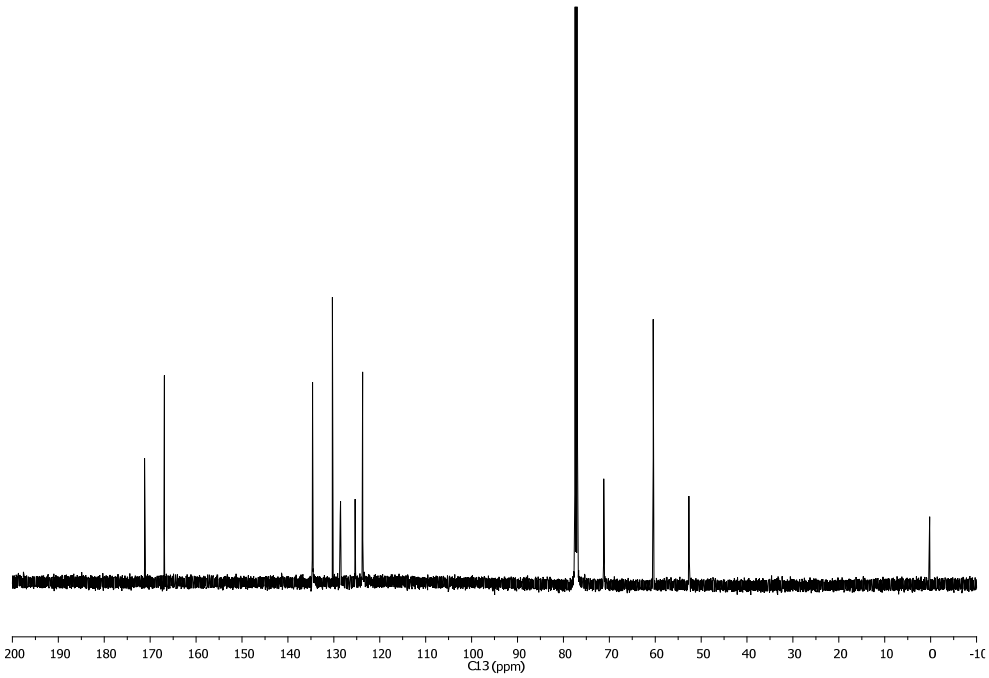
H1 (ppm)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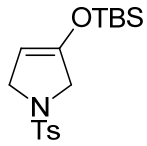
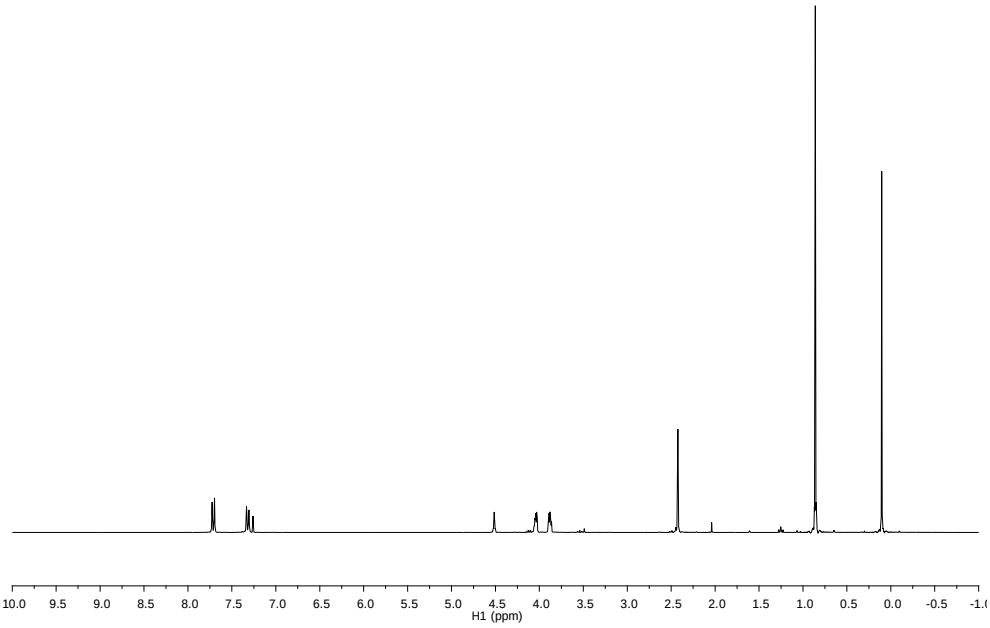
C13 (ppm)


OTBS
N
Ts

2.4l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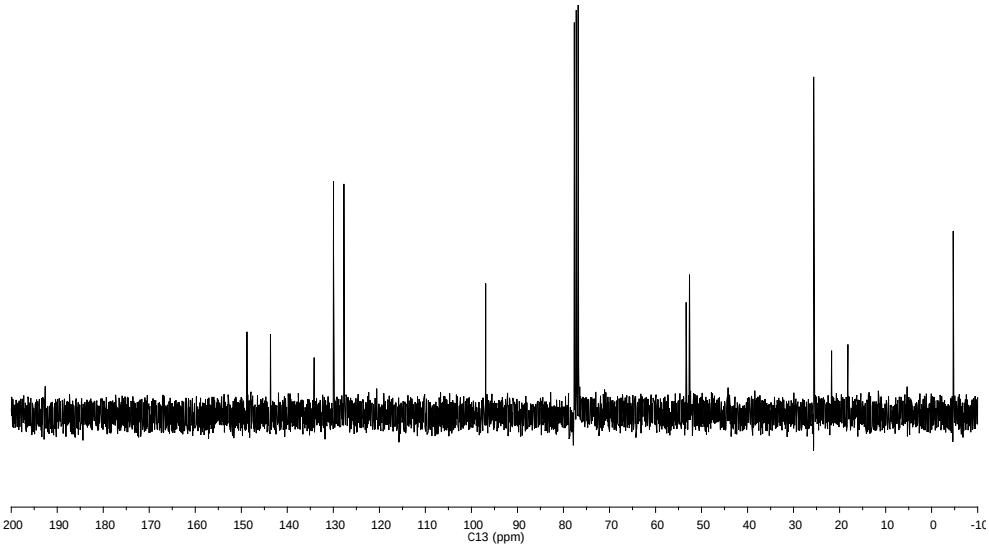
H1 (ppm)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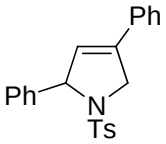
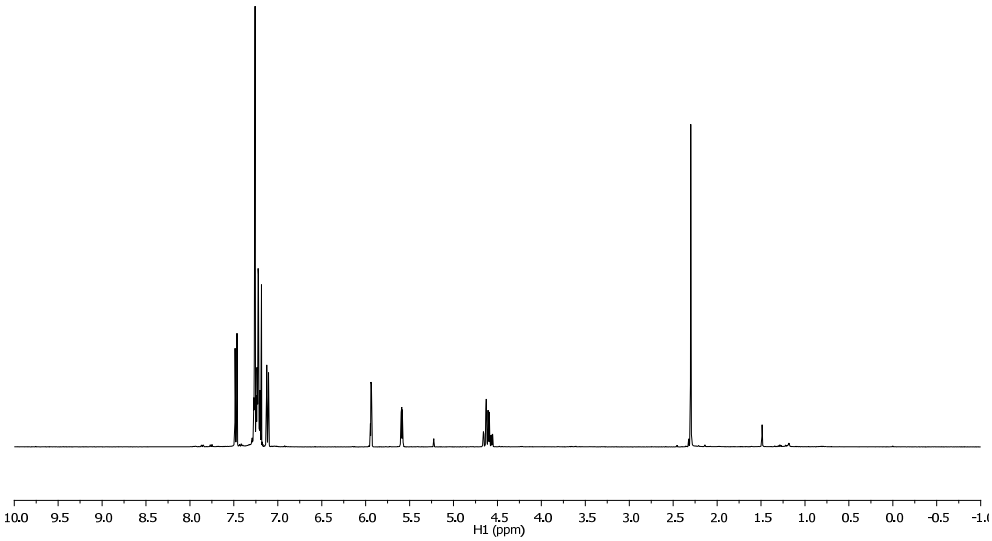
C13 (ppm)


Ph
Ph
N
Ts

2.4m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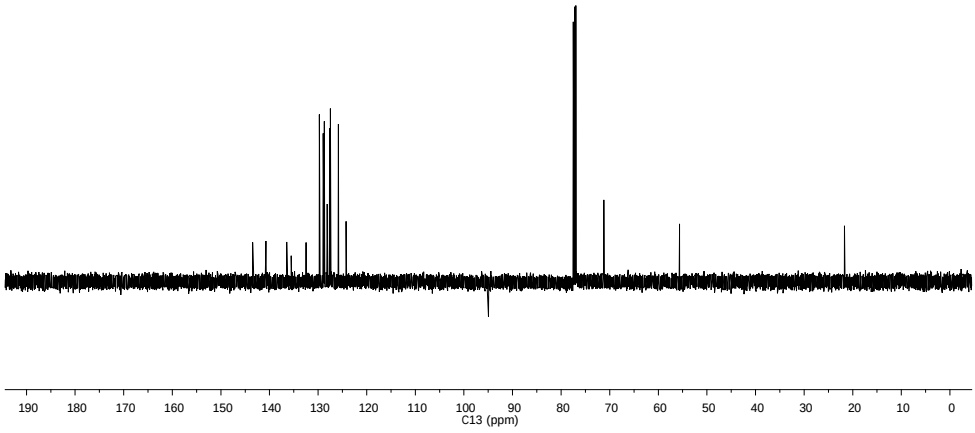
H1 (ppm)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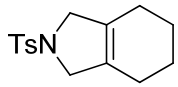
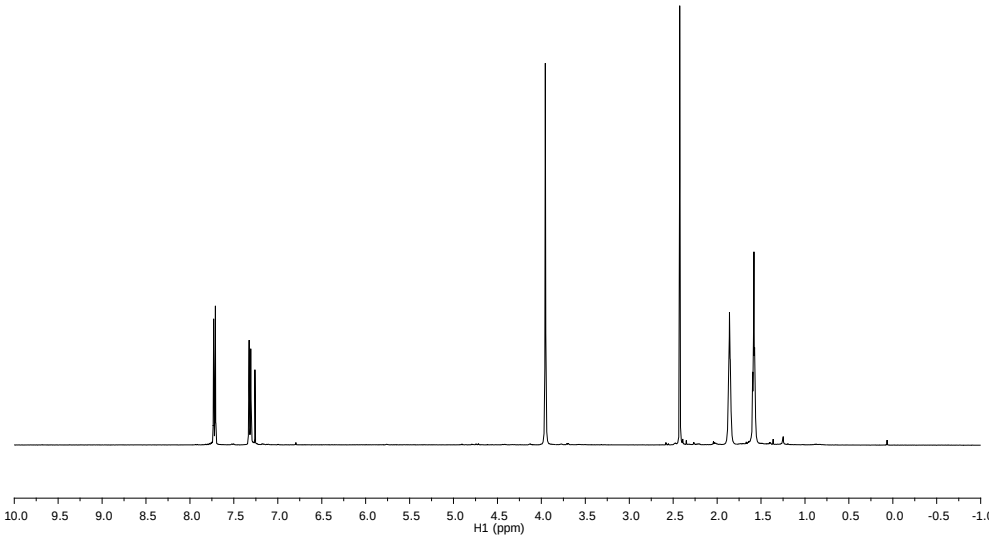
C13 (ppm)


TsN

2.4n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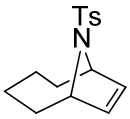
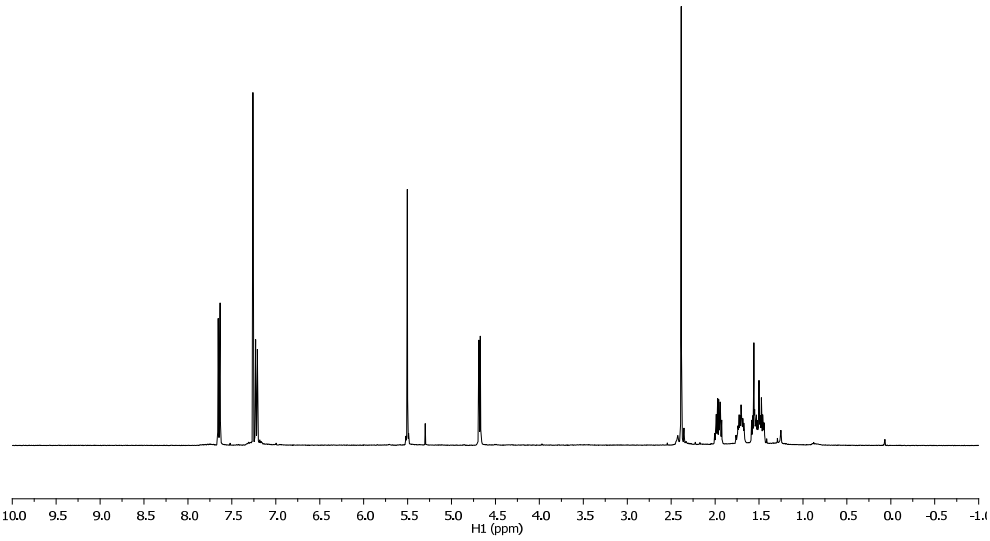
H1 (ppm)


Ts
N

2.4o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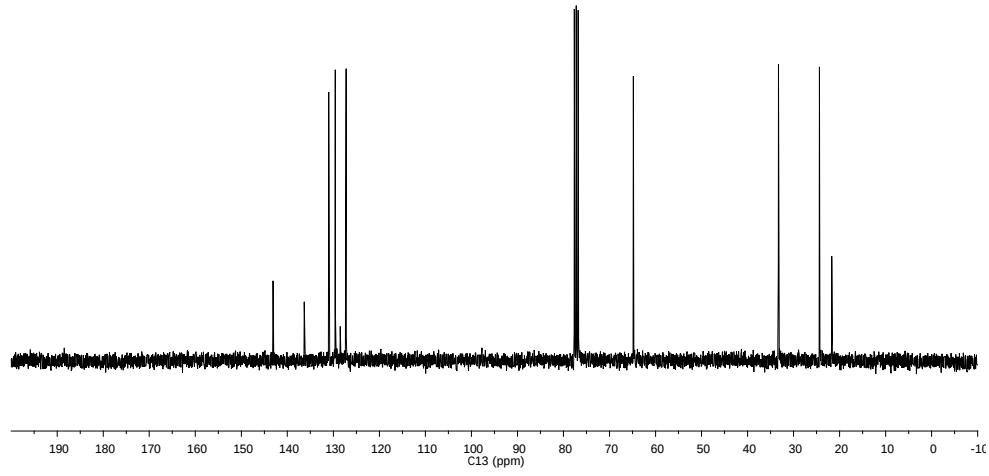
H1 (ppm)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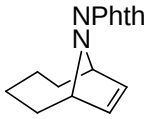
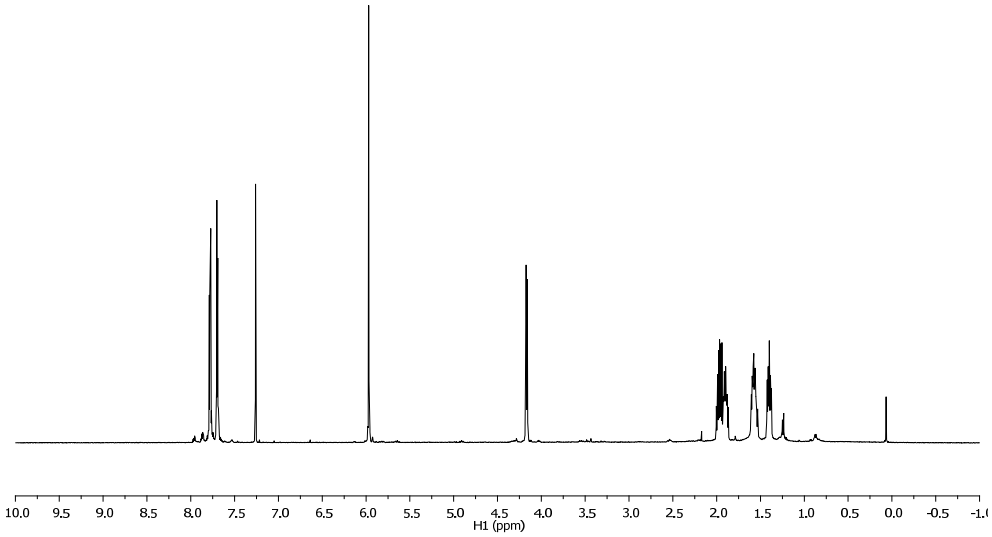
C13 (ppm)


NPhth
N

2.4p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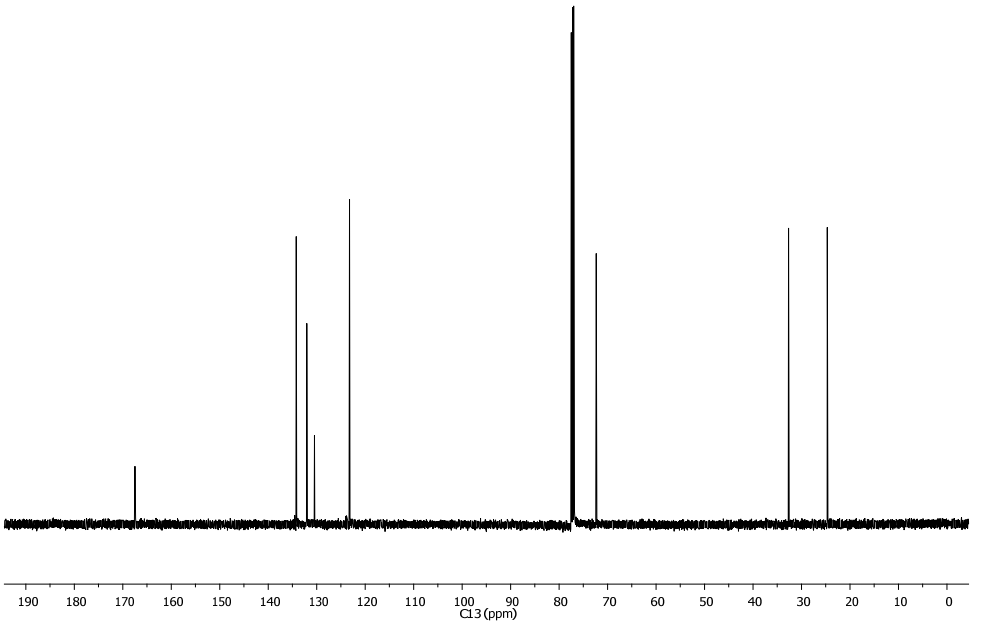
H1 (ppm)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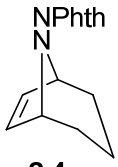
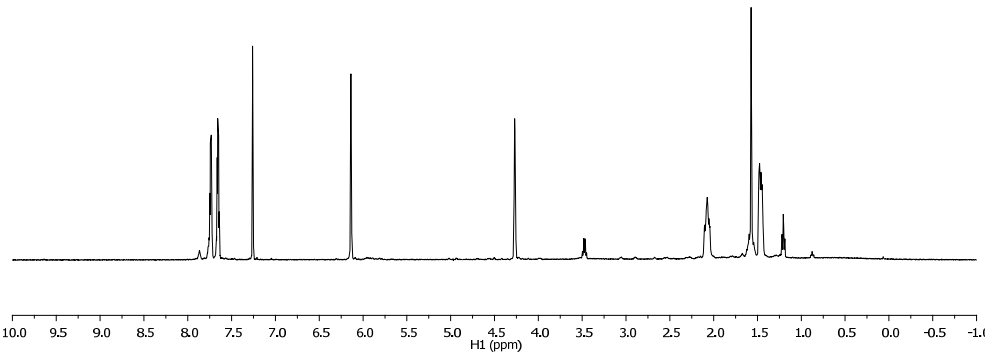

NPhth
N

2.4q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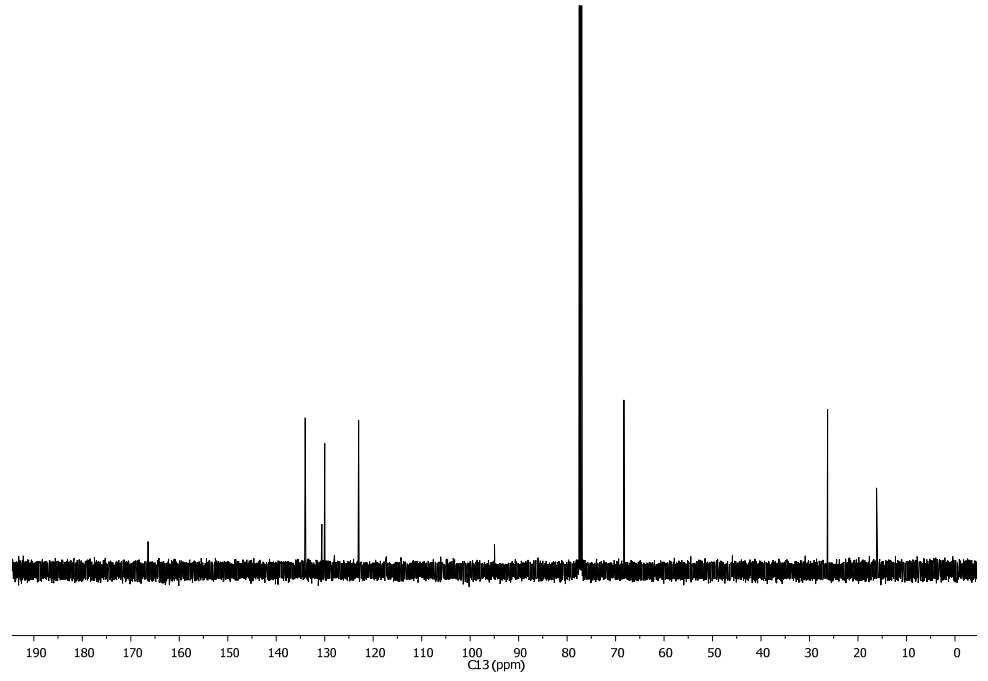
H1 (ppm)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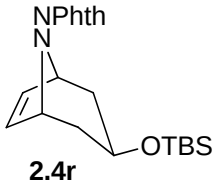
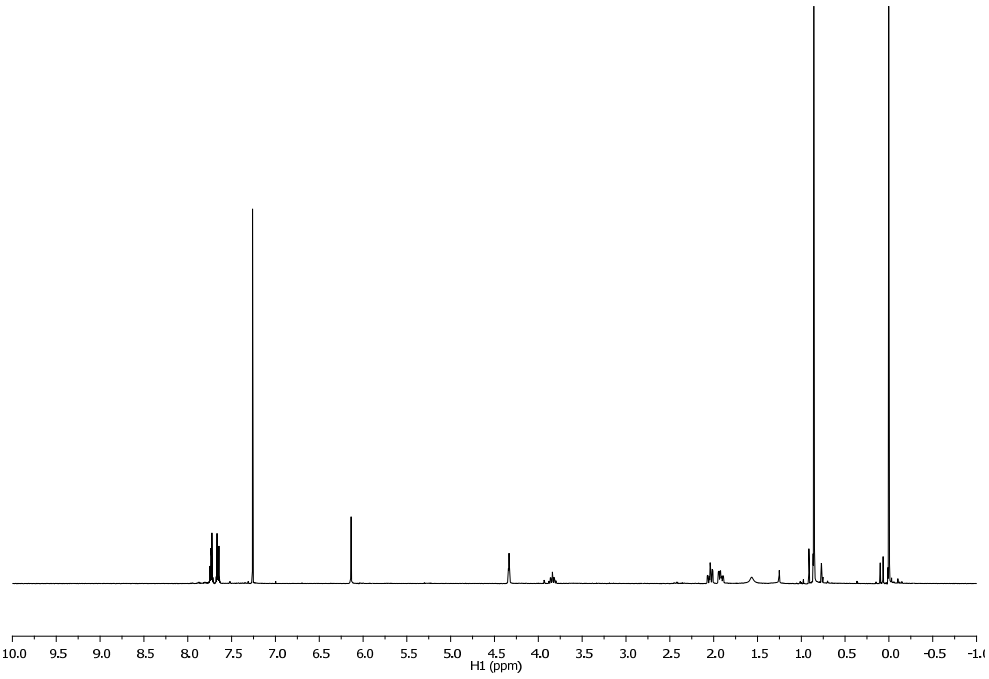
C13 (ppm)


NPhth
N
OTBS

2.4r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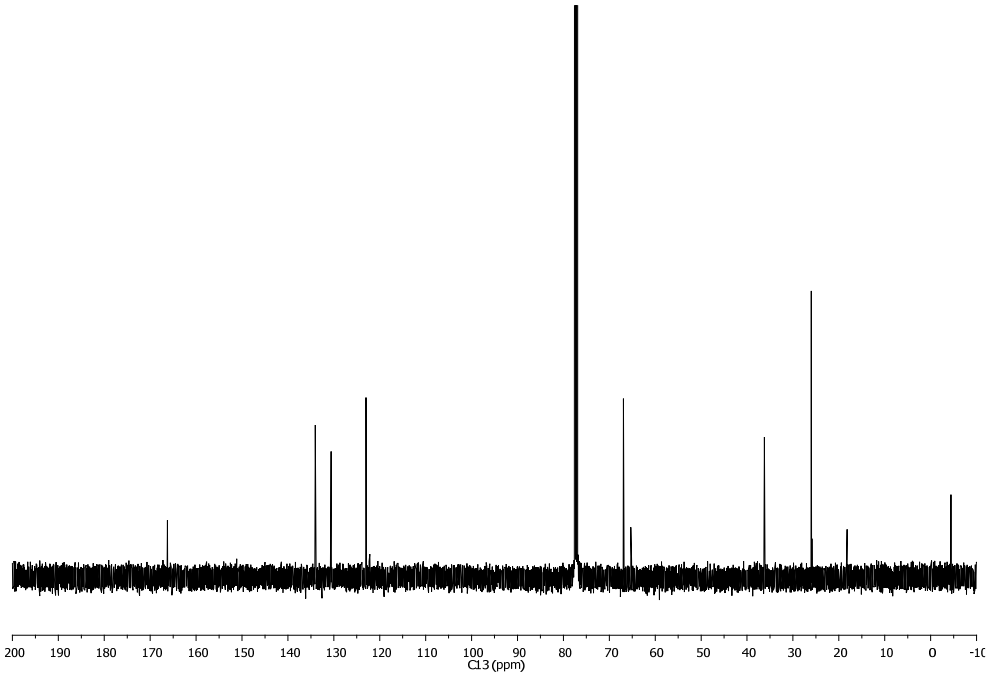
H1 (ppm)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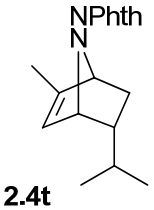
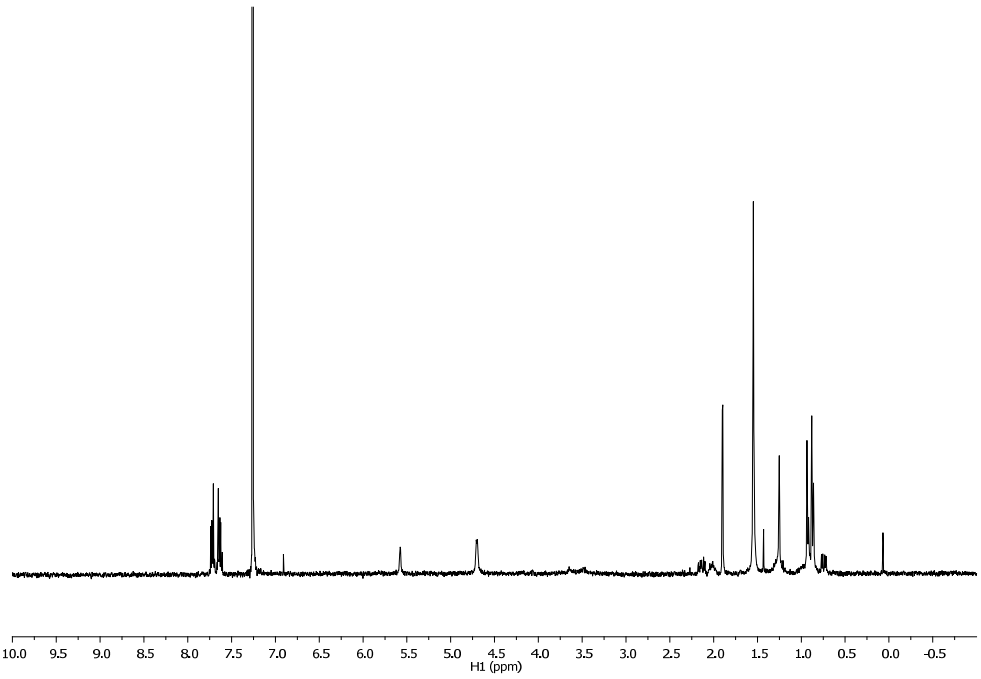
C13 (ppm)


NPhth
N

2.4t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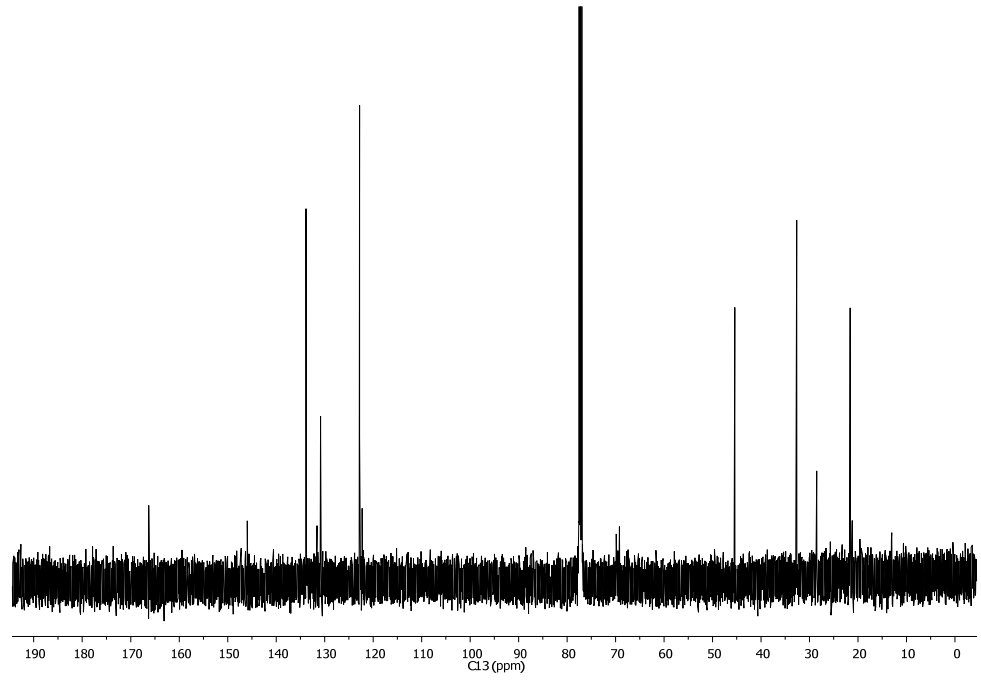
H1 (ppm)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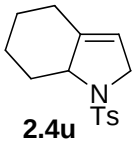
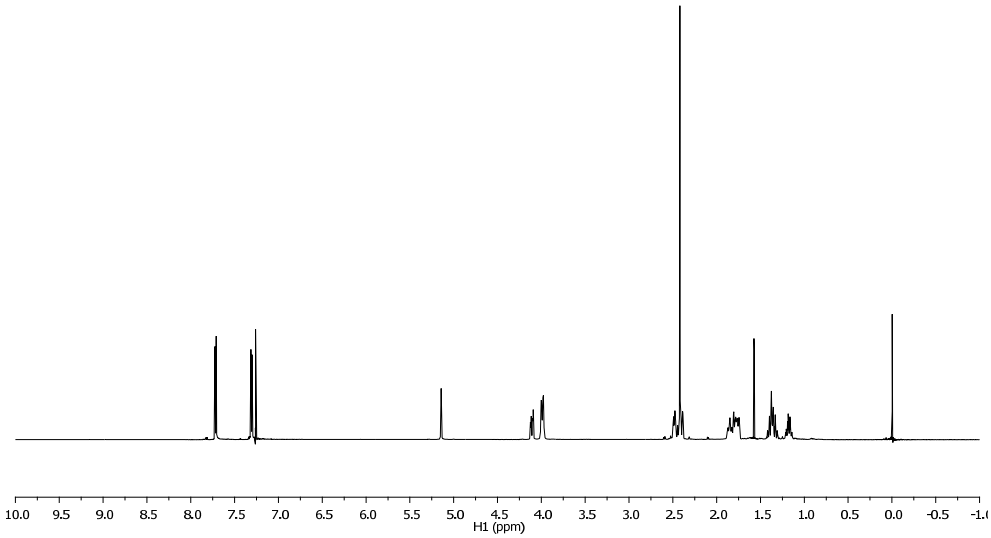
C13 (ppm)


N
Ts

2.4u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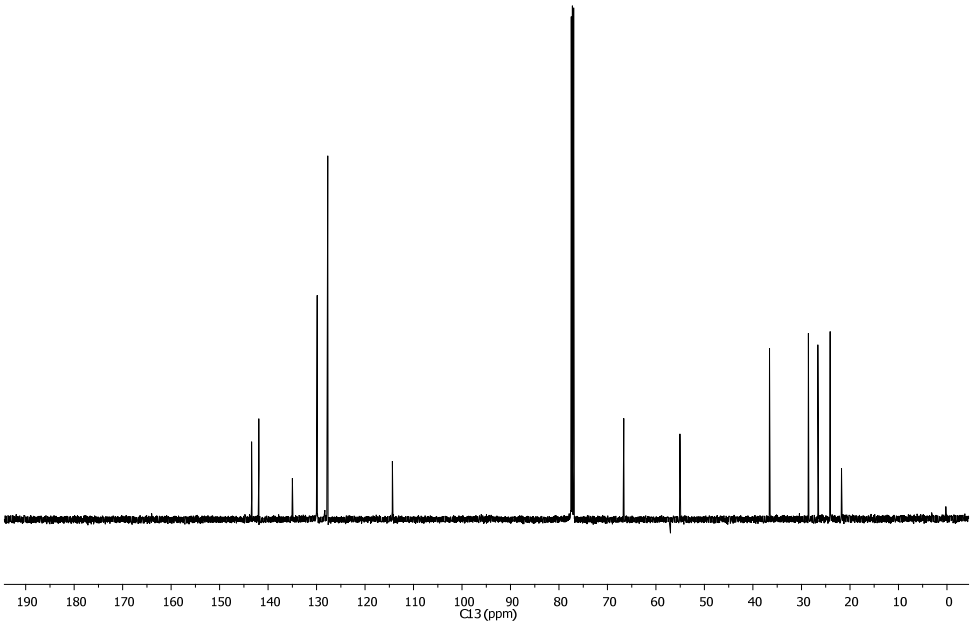
H1 (ppm)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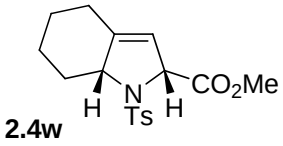
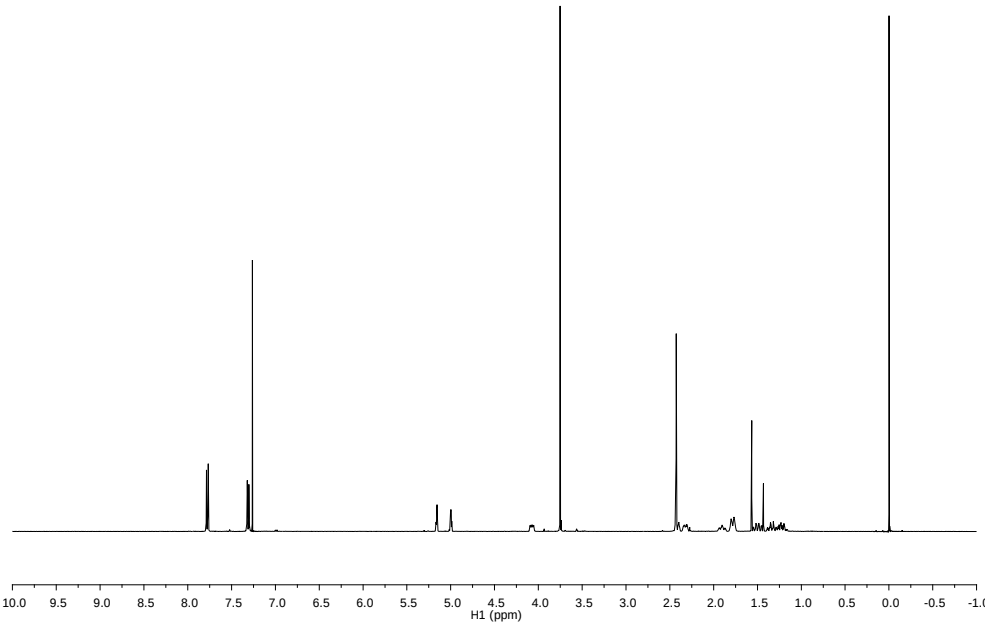

CO2Me
H
N
Ts
H

2.4w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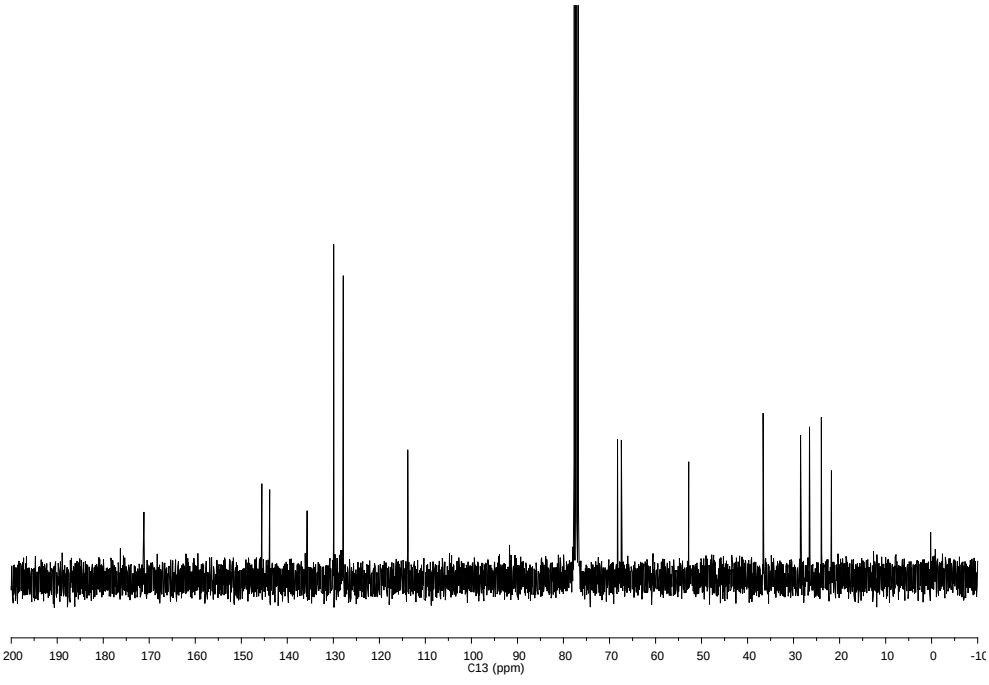
H1 (ppm)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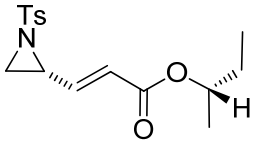
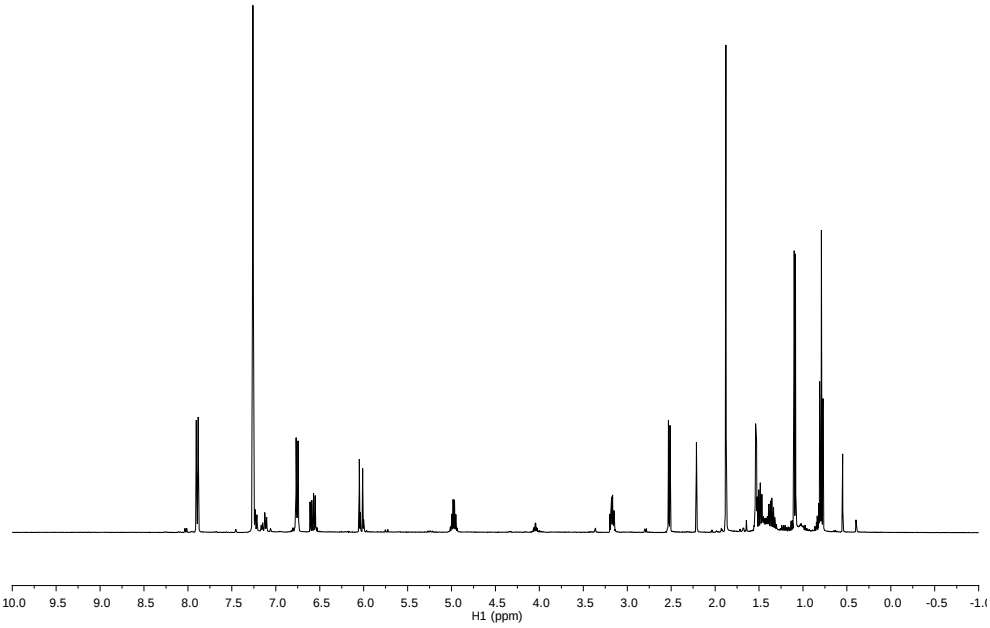
C13 (ppm)


Ts
N
O
O
H

2.31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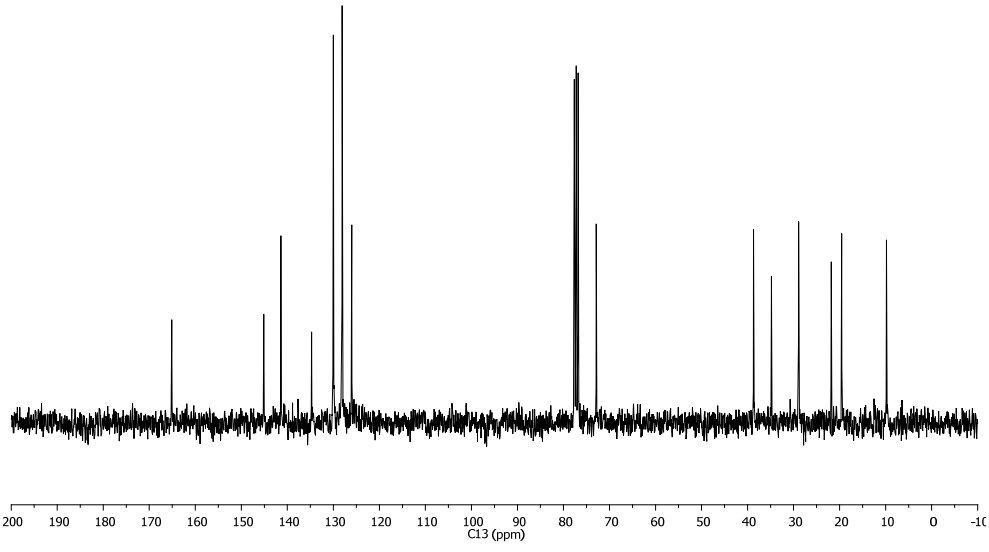
H1 (ppm)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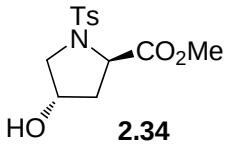
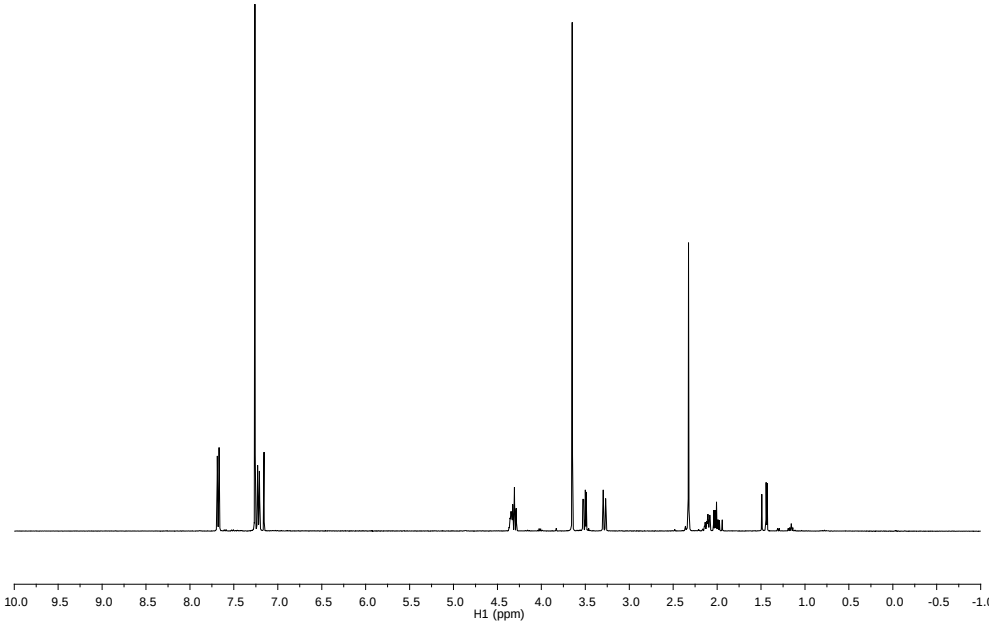

Ts
N
CO2Me
HO

2.34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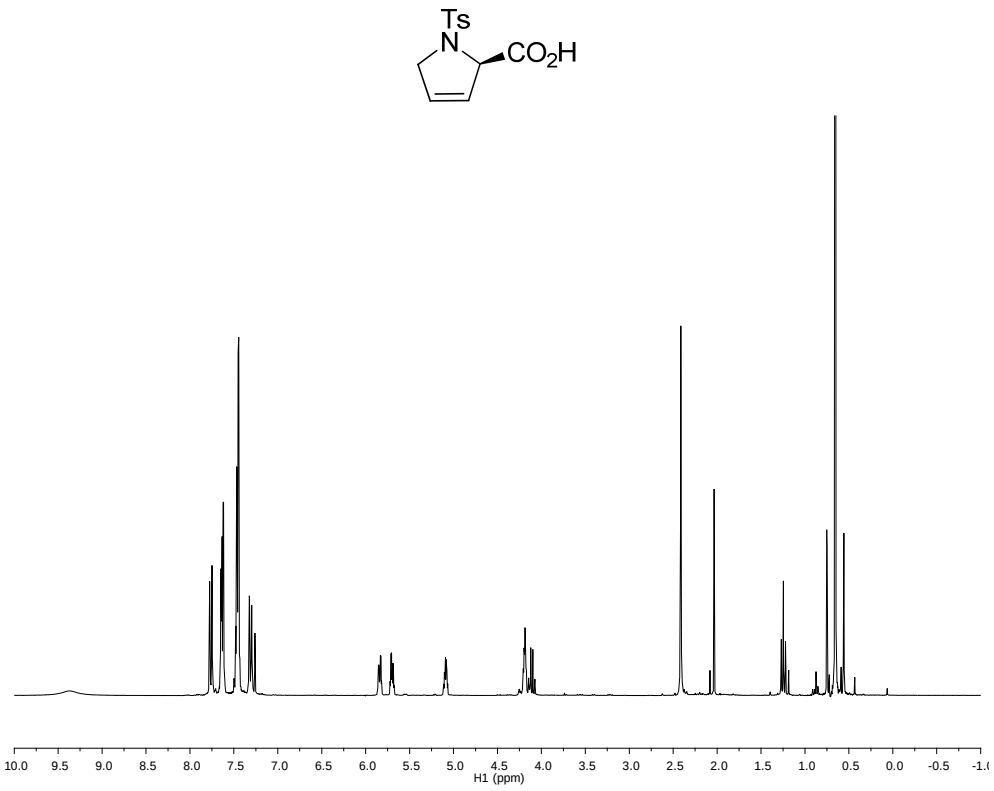
H1 (ppm)


Ts
N
CO2H
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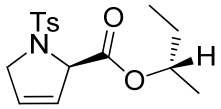
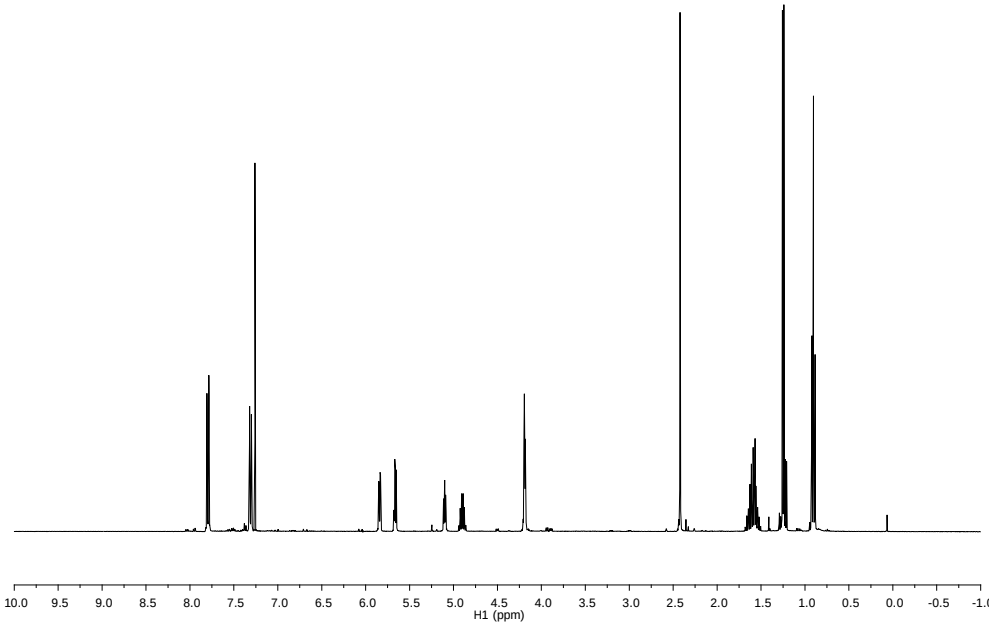
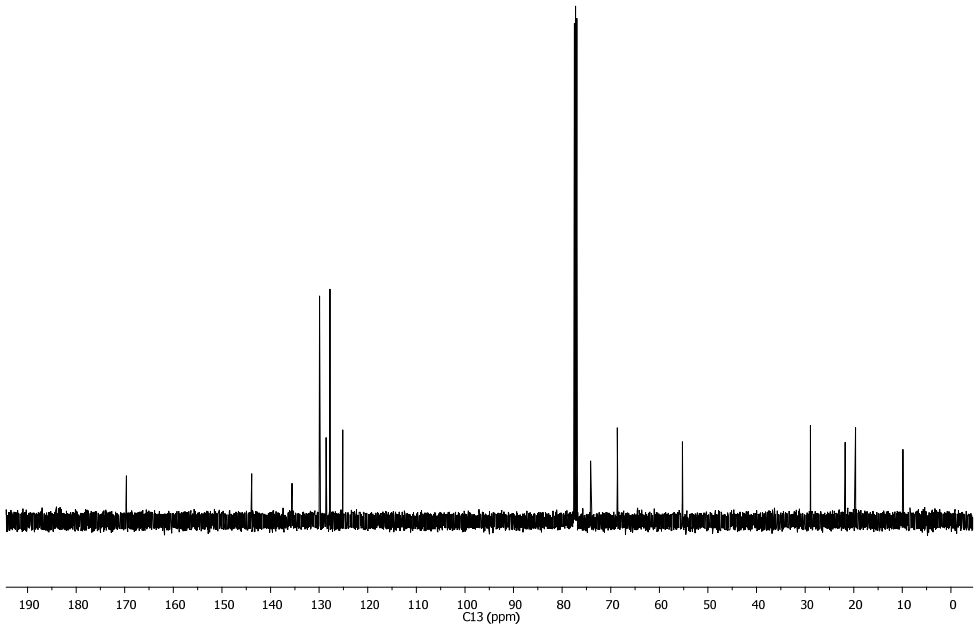
H1 (ppm)


Ts
N
O
O
H

2.35


10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
H1 (ppm)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C13 (ppm)

A2.3 Crystal Structure Data for Chapter 2

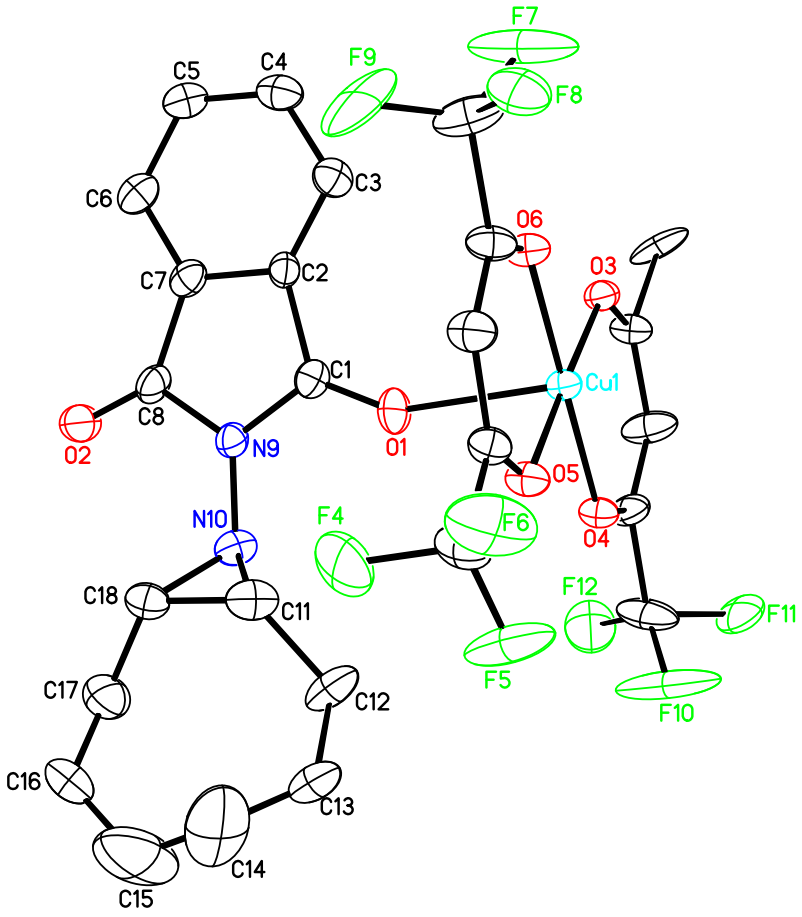

Figure A2.1: Crystal Structure of Monomer: Copper(II) bis(1,1,1,5,5,5-hexafluoroacetylacetonato):N-Phthalimido-9-aza-bicyclo [6.1.0] non-2-ene

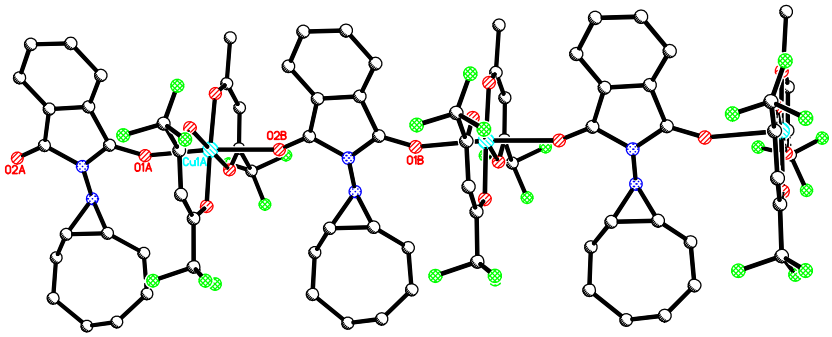

Figure A2.2: Crystal Structure of Chain

Table A2.1: Crystal Data and Structure Refinement

Empirical formula	C_{26} H_{19} Cu F_{12} N_2 O_6	Theta range for data collection	1.99 to 33.60°.
Formula weight	746.97	Index ranges	-23<=h<=24, -11<=k<=13, -32<=l<=32
Temperature	173(2) K	Reflections collected	20748
Wavelength	0.71073 Å	Independent reflections	9274 [R(int) = 0.0259]
Crystal system	Monoclinic	Completeness to theta = 33.60°	88.9 %
Space group	C2	Absorption correction	Semi-empirical from equivalents
Unit cell dimensions	a = 15.749(3) Å α = 90°	Max. and min. transmission	0.9190 and 0.6268
	b = 9.1568(18) Å β = 98.84(3)°	Refinement method	Full-matrix least-squares on F^2
	c = 20.736(4) Å γ = 90°.	Data / restraints / parameters	9274 / 1 / 510
Volume	2954.8(10) $Å^3$	Goodness-of-fit on F^2	1.046
Z	4	Final R indices [I>2sigma(I)]	R1 = 0.0461, wR2 = 0.1226
Density (calculated)	1.679 Mg/m^3	R indices (all data)	R1 = 0.0831, wR2 = 0.1389
Absorption coefficient	0.859 mm^{-1}	Absolute structure parameter	0.509(9)
F(000)	1496	Largest diff. peak and hole	0.707 and -0.643 $e.Å^{-3}$
Crystal size	0.60 x 0.20 x 0.10 mm^3		

Table A2.2: Atomic Coordinates and Equivalent Isotropic Displacement Pparameters

	x	y	z	U_{eq}		x	y	z	U_{eq}
Cu(1)	378(1)	3072(1)	2163(1)	30(1)	**C(1)**	320(1)	-699(2)	2033(1)	37(1)
F(4)	-1018(2)	1744(3)	4019(1)	115(1)	**C(2)**	-158(1)	-1136(2)	1381(1)	34(1)
F(5)	-108(1)	3453(4)	4209(1)	103(1)	**C(3)**	-566(1)	-367(2)	872(1)	43(1)
F(6)	-1441(2)	3909(4)	3976(1)	108(1)	**C(4)**	-959(1)	-1194(3)	337(1)	49(1)
F(4')	-666(4)	4480(5)	4045(2)	115(2)	**C(5)**	-955(1)	-2705(3)	324(1)	50(1)
F(5')	-275(3)	2327(6)	4204(2)	106(2)	**C(6)**	-548(1)	-3471(3)	857(1)	49(1)
F(6')	-1529(2)	2636(7)	3963(1)	97(2)	**C(7)**	-159(1)	-2649(2)	1393(1)	40(1)
F(1)	851(1)	3425(4)	109(1)	165(1)	**C(8)**	315(1)	-3216(2)	2003(1)	42(1)
F(2)	1959(1)	1923(2)	311(1)	101(1)	**N(9)**	542(1)	-1918(4)	2378(1)	35(1)
F(3)	2064(1)	4204(2)	339(1)	79(1)	**N(10)**	1124(1)	-1971(3)	2959(1)	40(1)
F(7)	-2237(2)	3532(7)	988(1)	131(3)	**C(11)**	808(1)	-1179(3)	3488(1)	53(1)
F(8)	-2859(2)	4161(4)	1738(2)	69(1)	**C(12)**	1443(2)	-214(3)	3896(1)	64(1)
F(9)	-2772(2)	1944(5)	1652(3)	120(2)	**C(13)**	1438(2)	-117(4)	4557(2)	115(1)
F(7')	-2284(2)	2022(4)	1054(1)	76(1)	**C(14)**	1118(3)	-1095(4)	4960(2)	134(1)
F(8')	-2968(1)	2837(9)	1765(1)	126(2)	**C(15)**	1432(3)	-2494(5)	5068(2)	153(2)
F(9')	-2384(2)	4265(4)	1228(2)	122(2)	**C(16)**	1314(3)	-3727(4)	4588(2)	106(1)
F(10)	3010(1)	3617(5)	3318(1)	146(2)	**C(17)**	1428(2)	-3664(3)	3939(2)	72(1)
F(11)	3595(1)	4169(3)	2563(1)	66(1)	**C(18)**	781(1)	-2770(3)	3487(1)	45(1)
F(12)	3519(2)	1912(3)	2665(2)	99(1)	**C(19)**	1547(1)	3226(4)	460(1)	61(1)
F(10')	3674(2)	2553(13)	2512(2)	209(5)	**C(20)**	1464(1)	3101(5)	1196(1)	38(1)
F(11')	3024(2)	2185(6)	3307(2)	86(1)	**C(21)**	2212(1)	3153(5)	1643(1)	58(1)
F(12')	3264(3)	4198(5)	2998(2)	102(2)	**C(22)**	2195(1)	3103(5)	2308(1)	41(1)
O(1)	500(1)	530(1)	2234(1)	54(1)	**C(23)**	3064(1)	3082(7)	2759(1)	68(1)
O(2)	486(1)	-4419(2)	2206(1)	62(1)	**C(24)**	-2304(1)	3066(7)	1535(1)	67(1)
O(3)	706(1)	3110(3)	1303(1)	33(1)	**C(25)**	-1445(1)	3058(5)	2011(1)	40(1)
O(4)	1566(1)	3087(3)	2596(1)	34(1)	**C(26)**	-1483(1)	3117(5)	2672(1)	45(1)
O(5)	29(1)	3108(3)	3017(1)	38(1)	**C(27)**	-730(1)	3087(5)	3119(1)	36(1)
O(6)	-805(1)	3056(3)	1725(1)	37(1)	**C(28)**	-818(1)	3109(6)	3847(1)	56(1)

Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3).
U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

Table A2.3: Bond Lengths [Å] and Angles [°]

Bond lengths [Å]		Angles [°]		Angles [°]	
Cu(1)--O(3)	1.9313(10)	O(3)- Cu(1) -O(5)	177.79(11)	F(12')- C(23) -F(10)	47.4(4)
Cu(1)--O(5)	1.9327(10)	O(3)- Cu(1) -O(6)	86.66(4)	F(10')- C(23) -F(10)	133.1(3)
Cu(1)--O(6)	1.9427(10)	O(5)- Cu(1) -O(6)	92.39(4)	F(12')- C(23) -F(12)	131.4(3)
Cu(1)--O(4)	1.9470(10)	O(3)- Cu(1) -O(4)	92.94(4)	F(10')- C(23) -F(12)	32.7(5)
Cu(1)--O(2)#1	2.3040(18)	O(5)- Cu(1) -O(4)	88.01(4)	F(10)- C(23) -F(12)	124.1(3)
Cu(1)--O(1)	2.3390(15)	O(6)- Cu(1) -O(4)	179.59(4)	F(12')- C(23) -F(11)	50.3(4)
F(4)- -C(28)	1.351(6)	O(3)- Cu(1) -O(2)#1	89.35(9)	F(10')- C(23) -F(11)	68.0(5)
F(5)- -C(28)	1.286(3)	O(5)- Cu(1) -O(2)#1	88.73(10)	F(10)- C(23) -F(11)	96.8(4)
F(6)- -C(28)	1.286(4)	O(6)- Cu(1) -O(2)#1	94.91(9)	F(12)- C(23) -F(11)	99.86(18)
F(4')- -C(28)	1.331(7)	O(4)- Cu(1) -O(2)#1	85.14(9)	F(12')- C(23) -F(11')	102.3(4)
F(5')- -C(28)	1.264(5)	O(3)- Cu(1) -O(1)	92.58(9)	F(10')- C(23) -F(11')	103.6(6)
F(6')- -C(28)	1.258(4)	O(5)- Cu(1) -O(1)	89.50(10)	F(10)- C(23) -F(11')	58.3(3)
F(1)- -C(19)	1.2324(19)	O(6)- Cu(1) -O(1)	94.93(9)	F(12)- C(23) -F(11')	74.8(4)
F(2)- -C(19)	1.415(3)	O(4)- Cu(1) -O(1)	85.03(9)	F(11)- C(23) -F(11')	138.6(2)
F(3)- -C(19)	1.261(3)	O(2)#1- Cu(1) -O(1)	170.06(5)	F(12')- C(23) -C(22)	114.1(5)
F(7)- -C(24)	1.231(4)	C(1)- O(1) -Cu(1)	152.26(13)	F(10')- C(23) -C(22)	114.9(3)
F(8)- -C(24)	1.435(5)	C(8)- O(2) -Cu(1)#2	153.42(15)	F(10)- C(23) -C(22)	111.9(2)
F(9)- -C(24)	1.310(6)	C(20)- O(3) -Cu(1)	124.35(8)	F(12)- C(23) -C(22)	111.9(4)
F(7')- -C(24)	1.386(5)	C(22)- O(4) -Cu(1)	124.25(8)	F(11)- C(23) -C(22)	109.2(3)
F(8')- -C(24)	1.233(3)	C(27)- O(5) -Cu(1)	124.77(8)	F(11')- C(23) -C(22)	110.7(3)
F(9')- -C(24)	1.266(6)	C(25)- O(6) -Cu(1)	124.40(8)	F(8')- C(24) -F(7)	127.8(2)
F(10)- -C(23)	1.273(4)	O(1)- C(1) -N(9)	123.92(18)	F(8')- C(24) -F(9')	108.5(5)
F(11)- -C(23)	1.401(5)	O(1)- C(1) -C(2)	127.89(17)	F(7)- C(24) -F(9')	41.6(4)
F(12)- -C(23)	1.320(6)	N(9)- C(1) -C(2)	108.18(17)	F(8')- C(24) -F(9)	42.1(4)
F(10')- -C(23)	1.254(6)	C(3)- C(2) -C(7)	122.39(19)	F(7)- C(24) -F(9)	125.0(4)
F(11')- -C(23)	1.410(6)	C(3)- C(2) -C(1)	132.91(18)	F(9')- C(24) -F(9)	139.3(3)
F(12')- -C(23)	1.157(7)	C(7)- C(2) -C(1)	104.60(17)	F(8')- C(24) -F(7')	106.0(4)
O(1)- -C(1)	1.218(2)	C(2)- C(3) -C(4)	115.86(19)	F(7)- C(24) -F(7')	64.0(3)
O(2)- -C(8)	1.195(3)	C(5)- C(4) -C(3)	123.4(2)	F(9')- C(24) -F(7')	104.4(3)
O(2)- -Cu(1)#2	2.3040(18)	C(4)- C(5) -C(6)	119.7(2)	F(9)- C(24) -F(7')	70.6(4)
O(3)- -C(20)	1.2481(15)	C(5)- C(6) -C(7)	117.0(2)	F(8')- C(24) -F(8)	54.1(4)
O(4)- -C(22)	1.2344(16)	C(2)- C(7) -C(6)	121.5(2)	F(7)- C(24) -F(8)	99.8(4)
O(5)- -C(27)	1.2454(16)	C(2)- C(7) -C(8)	111.67(19)	F(9')- C(24) -F(8)	61.5(3)
O(6)- -C(25)	1.2463(16)	C(6)- C(7) -C(8)	126.7(2)	F(9)- C(24) -F(8)	96.1(2)
C(1)- -N(9)	1.343(3)	O(2)- C(8) -N(9)	123.3(2)	F(7')- C(24) -F(8)	140.8(2)
C(1)- -C(2)	1.498(2)	O(2)- C(8) -C(7)	133.6(2)	F(8')- C(24) -C(25)	117.57(19)
C(2)- -C(3)	1.347(3)	N(9)- C(8) -C(7)	103.08(18)	F(7)- C(24) -C(25)	113.6(2)
C(2)- -C(7)	1.385(2)	C(1)- N(9) -N(10)	124.7(3)	F(9')- C(24) -C(25)	109.6(4)
C(3)- -C(4)	1.406(3)	C(1)- N(9) -C(8)	112.19(13)	F(9)- C(24) -C(25)	109.9(4)
C(4)- -C(5)	1.384(3)	N(10)- N(9) -C(8)	120.9(3)	F(7')- C(24) -C(25)	110.0(3)
C(5)- -C(6)	1.381(3)	N(9)- N(10) -C(11)	111.99(16)	F(8)- C(24) -C(25)	109.2(3)
C(6)- -C(7)	1.404(3)	N(9)- N(10) -C(18)	112.77(16)	O(6)- C(25) -C(26)	129.33(12)
C(7)- -C(8)	1.462(3)	C(11)- N(10) -C(18)	59.21(12)	O(6)- C(25) -C(24)	112.82(12)
C(8)- -N(9)	1.434(4)	C(18)- C(11) -N(10)	61.06(18)	C(26)- C(25) -C(24)	117.79(13)
N(9)- -N(10)	1.3980(15)	C(18)- C(11) -C(12)	127.4(2)	C(25)- C(26) -C(27)	119.91(13)
N(10)--C(11)	1.466(3)	N(10)- C(11) -C(12)	116.15(19)	O(5)- C(27) -C(26)	129.03(12)
N(10)--C(18)	1.485(3)	C(13)- C(12) -C(11)	119.7(2)	O(5)- C(27) -C(28)	113.60(11)
C(11)--C(18)	1.458(3)	C(12)- C(13) -C(14)	128.6(3)	C(26)- C(27) -C(28)	117.30(12)
C(11)--C(12)	1.496(3)	C(13)- C(14) -C(15)	123.3(4)	F(6')- C(28) -F(5')	103.5(4)
C(12)--C(13)	1.375(4)	C(14)- C(15) -C(16)	126.0(3)	F(6')- C(28) -F(6)	54.9(3)
C(13)--C(14)	1.373(5)	C(17)- C(16) -C(15)	126.3(3)	F(5')- C(28) -F(6)	132.0(3)
C(14)--C(15)	1.379(5)	C(16)- C(17) -C(18)	116.7(3)	F(6')- C(28) -F(5)	133.8(2)
C(15)--C(16)	1.497(5)	C(11)- C(18) -N(10)	59.73(17)	F(5')- C(28) -F(5)	49.3(3)
C(16)--C(17)	1.386(5)	C(11)- C(18) -C(17)	121.5(2)	F(6)- C(28) -F(5)	111.2(4)
C(17)--C(18)	1.515(4)	N(10)- C(18) -C(17)	115.9(2)	F(6')- C(28) -F(4')	112.8(5)
C(19)--C(20)	1.556(2)	F(1)- C(19) -F(3)	108.8(3)	F(5')- C(28) -F(4')	106.2(4)
C(20)--C(21)	1.3836(18)	F(1)- C(19) -F(2)	113.1(2)	F(6)- C(28) -F(4')	60.3(4)
C(21)--C(22)	1.384(2)	F(3)- C(19) -F(2)	102.92(14)	F(5)- C(28) -F(4')	59.3(3)
C(22)--C(23)	1.5347(19)	F(1)- C(19) -C(20)	112.87(13)	F(6')- C(28) -F(4)	51.6(3)
C(24)--C(25)	1.547(2)	F(3)- C(19) -C(20)	113.6(2)	F(5')- C(28) -F(4)	59.0(4)
C(25)--C(26)	1.3809(19)	F(2)- C(19) -C(20)	105.2(2)	F(6)- C(28) -F(4)	104.7(3)
C(26)--C(27)	1.3894(18)	O(3)- C(20) -C(21)	128.30(13)	F(5)- C(28) -F(4)	106.8(3)
C(27)--C(28)	1.536(2)	O(3)- C(20) -C(19)	113.69(11)	F(4')- C(28) -F(4)	145.9(3)
		C(21)- C(20) -C(19)	117.61(13)	F(6')- C(28) -C(27)	113.6(2)
Symmetry transformations used to generate equivalent atoms: #1 x,y+1,z #2 x,y-1,z		C(20)- C(21) -C(22)	121.40(14)	F(5')- C(28) -C(27)	114.4(3)
		O(4)- C(22) -C(21)	128.59(12)	F(6)- C(28) -C(27)	113.6(3)
		O(4)- C(22) -C(23)	114.25(12)	F(5)- C(28) -C(27)	112.02(17)
		C(21)- C(22) -C(23)	117.15(13)	F(4')- C(28) -C(27)	106.1(4)
		F(12')- C(23) -F(10')	109.9(6)	F(4)- C(28) -C(27)	107.9(3)

Table A2.4: Anisotropic Displacement Parameters

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cu(1)	27(1)	35(1)	27(1)	-1(1)	2(1)	-1(1)
F(4)	189(3)	106(2)	51(1)	23(1)	27(2)	-42(2)
F(5)	50(1)	224(4)	35(1)	-32(2)	8(1)	-39(2)
F(6)	132(2)	133(2)	58(2)	-25(2)	16(2)	61(2)
F(4')	206(5)	93(3)	56(2)	-33(2)	47(3)	-34(3)
F(5')	79(2)	202(5)	38(2)	43(2)	20(2)	56(3)
F(6')	40(1)	219(7)	39(1)	33(2)	26(1)	6(2)
F(1)	44(1)	413(3)	39(1)	81(1)	4(1)	18(2)
F(2)	195(2)	65(1)	56(1)	-33(1)	57(1)	-23(1)
F(3)	62(1)	120(1)	59(1)	2(1)	20(1)	-19(1)
F(7)	28(1)	334(8)	31(1)	29(3)	4(1)	12(2)
F(8)	47(1)	83(2)	72(2)	12(2)	-3(1)	20(1)
F(9)	26(1)	105(3)	212(5)	-58(3)	-35(2)	1(2)
F(7')	49(1)	129(2)	46(1)	-43(1)	-7(1)	2(2)
F(8')	27(1)	301(6)	50(1)	0(4)	11(1)	-12(3)
F(9')	94(2)	89(2)	155(3)	29(2)	-75(2)	16(2)
F(10)	45(1)	356(7)	32(1)	-29(2)	-9(1)	-11(2)
F(11)	41(1)	86(2)	65(1)	-8(1)	-10(1)	-24(1)
F(12)	46(1)	89(2)	148(3)	28(2)	-32(2)	2(1)
F(10')	38(2)	546(16)	43(2)	-6(5)	4(2)	70(5)
F(11')	41(2)	168(4)	42(2)	44(2)	-11(2)	5(2)
F(12')	90(3)	104(3)	94(3)	1(3)	-44(2)	-52(2)
O(1)	75(1)	21(1)	62(1)	-1(1)	1(1)	1(1)
O(2)	83(1)	33(1)	60(1)	-1(1)	-21(1)	3(1)
O(3)	29(1)	41(1)	28(1)	2(1)	1(1)	-5(1)
O(4)	28(1)	44(1)	29(1)	2(1)	1(1)	4(1)
O(5)	33(1)	52(1)	29(1)	3(1)	3(1)	2(1)
O(6)	29(1)	53(1)	28(1)	-4(1)	2(1)	3(1)
C(1)	35(1)	34(1)	42(1)	-5(1)	9(1)	0(1)
C(2)	33(1)	30(1)	38(1)	2(1)	6(1)	-4(1)
C(3)	45(1)	41(1)	44(1)	0(1)	8(1)	8(1)
C(4)	35(1)	74(1)	38(1)	9(1)	7(1)	3(1)
C(5)	45(1)	60(1)	44(1)	-7(1)	-2(1)	1(1)
C(6)	43(1)	50(1)	52(1)	-13(1)	7(1)	-4(1)
C(7)	33(1)	47(1)	41(1)	-5(1)	9(1)	-7(1)
C(8)	46(1)	29(1)	50(1)	-10(1)	1(1)	-2(1)
N(9)	35(1)	28(1)	41(1)	-1(2)	1(1)	1(2)
N(10)	34(1)	43(1)	42(1)	-8(2)	2(1)	10(1)
C(11)	49(1)	63(1)	45(1)	-9(1)	4(1)	18(1)
C(12)	52(1)	81(2)	57(1)	-34(1)	6(1)	-18(1)
C(13)	161(3)	82(2)	78(2)	-4(2)	-55(2)	-47(2)
C(14)	206(3)	112(2)	106(2)	-57(2)	91(2)	-40(2)
C(15)	264(5)	134(4)	58(2)	-13(2)	15(3)	47(3)
C(16)	151(3)	96(2)	60(2)	39(2)	-19(2)	-37(2)
C(17)	92(2)	54(2)	63(2)	7(1)	-6(2)	5(1)
C(18)	41(1)	54(1)	41(1)	3(1)	2(1)	8(1)
C(19)	33(1)	113(2)	38(1)	-47(1)	5(1)	-20(1)
C(20)	32(1)	53(1)	29(1)	1(2)	0(1)	6(2)
C(21)	30(1)	108(2)	34(1)	-9(2)	3(1)	-9(2)
C(22)	29(1)	57(1)	35(1)	-2(2)	-1(1)	-11(2)
C(23)	28(1)	132(2)	41(1)	24(3)	-3(1)	8(3)
C(24)	33(1)	118(2)	48(1)	-23(3)	-2(1)	2(3)
C(25)	32(1)	54(1)	34(1)	-3(2)	1(1)	15(2)
C(26)	33(1)	66(1)	38(1)	6(2)	8(1)	-3(2)
C(27)	36(1)	42(1)	31(1)	0(2)	6(1)	6(2)
C(28)	47(1)	84(1)	39(1)	15(2)	12(1)	1(3)

Anisotropic displacement parameters ($Å^2 x\ 10^3$). The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + \ldots + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

Table A2.5: Hydrogen Coordinates and Isotropic Displacement Parameters

H(3A)	-587	670	874	52
H(4A)	-1242	-689	-36	59
H(5A)	-1231	-3213	-50	60
H(6A)	-533	-4509	860	58
H(10A)	1711	-1993	2942	48
H(11A)	233	-712	3355	63
H(12A)	1849	329	3699	77
H(13A)	1688	742	4762	138
H(14A)	496	-1192	4795	161
H(14B)	1165	-623	5393	161
H(15A)	1205	-2849	5459	184
H(15B)	2060	-2389	5199	184
H(16A)	1696	-4518	4786	127
H(16B)	719	-4080	4585	127
H(17A)	1418	-4675	3769	86
H(17B)	2007	-3262	3921	86
H(18A)	200	-3220	3364	55
H(21A)	2749	3224	1490	69
H(26A)	-2023	3177	2820	54

Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3)

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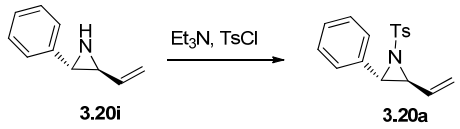
APPENDIX 3

A3.1 Experimental Procedures for Chapter 3

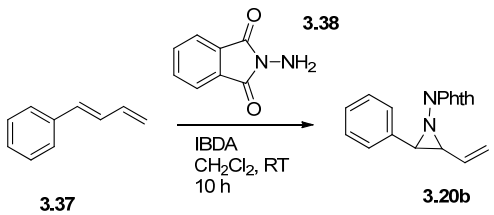
General Information: Commercial reagents were purchased and used without further purification. All glassware was flame dried and reactions were performed under a nitrogen atmosphere, unless otherwise stated. Toluene, benzene, dichloromethane, diethyl ether, and THF were dried over a column of alumina. Flash chromatography was done with Silicycle SiliaFlash® F60 silica, and thin layer chromatography (TLC) was performed with EMD 250 μm silica gel 60-F_{254} plates. ^{1}H and ^{13}C NMR data was acquired on a Varian Inova 400, 500, or 600 (400, 500 or 600 MHz) or an ARX 300 Bruker (300 MHz) spectrometer and referenced to residual protic solvent. IR spectra were taken on a Mattson Instruments Research Series FTIR spectrometer. High-resolution mass spectrometry was performed at the University of Illinois at Urbana-Champaign facility. Enantiomeric ratios were determined on an HP 1100 Series HPLC with a Daicel Chiracel® OD-H (0.46 cm x 25 cm) column. Measurements of optical rotation were done on a Rudolph Research Analytic Autopol III Automatic Polarimeter.



3.20i **3.20a**

2-Phenyl-1-tosyl-3-vinylaziridine (**3.20a**): To a solution of aziridine **3.20i** (0.040 mmol, in CH_2Cl_2 and THF as described below) was added *p*-toluenesulfonyl chloride (11.5 mg, 0.060 mmol, 1.5 equiv.). Lastly, triethylamine (0.025 mL, 18.2 mg, 0.18 mmol, 4.5 equiv.) was added and the reaction was stirred for 12 hours at room temperature. The reaction is concentrated and then purified by chromatography on silica gel to yield aziridine **3.20a** (4.4 mg, 37%). This aziridine has previously been prepared and characterized as a cis/trans mixture.[1]

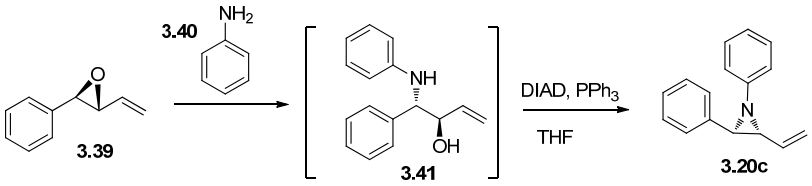
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.84 (d, *J* = 8.3, 2H), 7.29 – 7.24 (m, 5H), 7.17 (dd, *J* = 7.6, 1.8, 2H), 6.33 (dt, *J* = 17.0, 10.0, 1H), 5.57 (d, *J* = 17.0, 1H), 5.48 (d, *J* = 10.3, 1H), 4.05 (d, *J* = 4.0, 1H), 3.30 (dd, *J* = 9.7, 4.1, 1H), 2.40 (s, 3H). **^{13}C NMR** (151 MHz, $CDCl_3$) δ 144.4, 137.2, 135.2, 131.3, 129.8, 128.8, 128.5, 127.7, 126.5, 123.0, 55.3, 48.7, 21.8. **IR** (neat) 3064, 3032, 1598, 1455, 1328, 1161, 1089, 892, 717, 576 m^{-1}.



3.37 **3.20b**

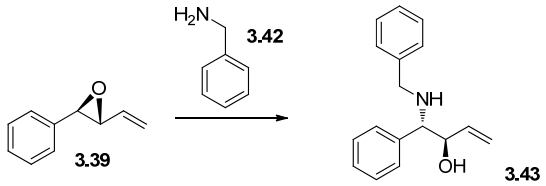
cis/trans-N-Phthalimido-2-phenyl-3-vinylaziridine (**3.20b**): trans-1-phenyl-butadiene[2] (0.50g, 3.8 mmol, 1 equiv.) was dissolved in dry CH_2Cl_2 (40 mL, 0.1 M) and N-amino-phthalimide (1.25 g, 7.68 mmol, 2.0 equiv.) was added. The heterogeneous solution was stirred vigorously while iodobenzenediacetate (1.86 g, 7.68 mmol, 1.0 equiv.) was added portion wise over 15 minutes. The solution was stirred at room temperature for 14 hours. The reaction was diluted with CH_2Cl_2, washed with sat. $NaHCO_3$, and dried over Na_2SO_4. The solvent was evaporated and crude mixture purified by flash chromatography to yield aziridine **3.20b** (0.716 g, 64%). This aziridine has previously been prepared using an alternative method and characterized.[3]

Major invertomer: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.80 (dd, *J* = 5.5, 3.0, 2H), 7.70 (dd, *J* = 5.5, 3.0, 2H), 7.49 – 7.44 (m, 2H), 7.42 – 7.32 (m, 3H), 5.78 (ddd, *J* = 17.1, 10.4, 7.9, 1H), 5.56 (ddd, *J* = 17.1, 1.1, 0.6, 1H), 5.37 (dd, *J* = 10.3, 1.1, 1H), 4.20 (d, *J* = 5.4, 1H), 3.42 (dd, *J* = 7.9, 5.4, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.9 136.4, 134.3, 130.7, 130.6, 128.8, 128.3, 127.2, 123.3, 122.4, 52.2, 48.6. **IR** (neat) 3191, 1772, 1716, 1604, 1467, 1374, 1307, 1052, 712 cm^{-1}.

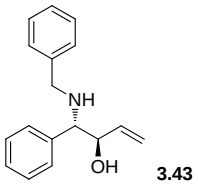


1,2-Diphenyl-3-vinylaziridine (**3.20c**): 2-phenyl-3-vinyloxirane[4] (0.10 g, 0.68 mmol, 1 equiv.) was heated neat in aniline (0.50 mL, 0.51 g, 5.49 mmol, 8 equiv.) at 85°C for 6 days. The amino alcohol can be isolated by silica gel chromatography but was used crude in the next step. The amino alcohol has been synthesized by an alternate route and characterized previously.[5] To the crude amino alcohol was added THF (12 mL, 0.05 M) and PPh_3 (0.54 g, 2.05 mmol, 3 equiv.). Lastly, diisopropyl azodicarboxylate (0.40 mL, 0.42 g, 2.05 mmol, 3 equiv.) is added slowly and the reaction is stirred for 40 hours at room temperature. The reaction is concentrated and purified by chromatography on silica gel to yield aziridine **3.20c** (0.065 g, 43%). This aziridine has previously been prepared using an alternative method and characterized.[6]

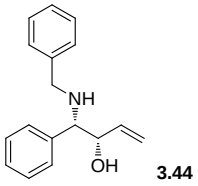
^{1}H NMR (400 MHz,CDC) δ 7.39 – 7.30 (m, 4H), 7.30 – 7.17 (m, 3H), 6.99 – 6.91 (m, 3H), 5.52 – 5.40 (m, 1H), 5.29 – 5.15 (m, 2H), 3.26 (d, *J* = 2.7, 1H), 3.12 – 3.01 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.8, 138.5, 134.8, 129.0, 128.6, 127.6, 126.4, 122.3, 120.9, 119.4, 51.2, 48.1. **IR** (neat) 3062, 1597, 1488, 1455, 1430, 1395, 1310, 1265, 1154, 987, 905, 758, 695 cm^{-1}. **HRMS** (ESI) m/z 222.1286 [calculated mass for $C_{16}H_{16}N$ ($M+H^+$) 222.1283].



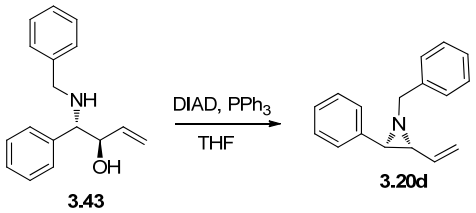
anti-1-(Benzylamino)-1-phenylbut-3-en-2-ol: 2-phenyl-3-vinyloxirane[7] (0.079 g, 0.54 mmol, 1 equiv.) was heated neat in benzylamine (0.50 mL, 0.49 g, 4.58 mmol, 8.5 equiv.) at 85°C for 2 days. The crude reaction was loaded on to a column of silica gel and amino alcohol can be isolated by silica gel chromatography to anti amino alcohol (0.128 g, 93%). A small amount of the syn amino alcohol was isolated and characterized presumably from the vinyloxirane starting material not being completely isomerically pure.



anti-1-(Benzylamino)-1-phenylbut-3-en-2-ol:
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34 – 7.20 (m, 5H), 5.57 (ddd, *J* = 17.3, 10.3, 8.3, 1H), 5.21 (dd, *J* = 10.3, 1.6, 1H), 5.13 – 5.08 (m, 1H), 4.69 (d, *J* = 5.1, 1H), 3.82 (d, *J* = 13.3, 1H), 3.66 (d, *J* = 13.3, 1H), 3.32 (dd, *J* = 8.2, 5.1, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.9, 140.1, 136.7, 128.6, 128.3(0), 128.2(9), 127.7, 127.3, 126.9, 119.1, 74.6, 66.4, 51.1. **IR** (neat) 3420, 3026, 1493, 1452, 1027, 991, 921, 748, 697 cm^{-1}. **HRMS** (ESI) m/z 254.1539 [calculated mass for $C_{17}H_{20}NO$ ($M+H^+$) 254.1545].



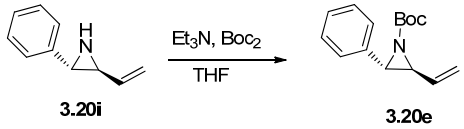
syn-1-(Benzylamino)-1-phenylbut-3-en-2-ol:
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.23 (m, 10H), 5.65 (ddd, *J* = 17.2, 10.5, 5.8, 1H), 5.28 (dt, *J* = 17.2, 1.6, 1H), 5.17 – 5.13 (m, 1H), 4.29 – 4.25 (m, 1H), 3.82 (d, *J* = 5.2, 1H), 3.76 (d, *J* = 13.1, 1H), 3.59 (d, *J* = 13.1, 1H), 2.71 (bs, 1H), 1.95 (bs, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 140.2, 139.4, 137.0, 128.7, 128.6, 128.4, 128.2, 127.8, 127.3, 117.3, 75.3, 66.3, 51.3. **IR** (neat) 3326, 3026, 2847, 1652, 1439, 1453, 1363, 1116, 1027, 992, 924, 683 cm^{-1}. **HRMS** (ESI) m/z 254.1537 [calculated mass for $C_{17}H_{20}NO$ ($M+H^+$) 254.1545].



3.43 3.20d

trans-1-Benzyl-2-phenyl-3-vinylaziridine (**3.20d** *trans*): To anti-1-(benzylamino)-1-phenylbut-3-en-2-ol (0.045 g, 0.178 mmol, 1 equiv.) was added THF (2 mL, 0.1 M) and PPh_3 (0.070 g, 0.27 mmol, 1.5 equiv.). Lastly, diisopropyl azodicarboxylate (0.050 mL, 0.053 g, 0.26 mmol, 1.5 equiv.) is added slowly and the reaction is stirred for 10 hours at room temperature. The reaction is concentrated and purified by chromatography on silica gel to yield aziridine **3.20d** (22.5 mg, 57%). This aziridine has previously been prepared using an alternative method but not characterized.[8]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.18 (m, 5H), 5.96 (dt, *J* = 16.9, 9.7, 1H), 5.49 – 5.42 (m, 1H), 5.35 (dd, *J* = 10.3, 1.1, 1H), 4.02 (d, *J* = 14.2, 1H), 3.79 (d, *J* = 14.3, 1H), 2.77 – 2.71 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 139.9(3), 139.8(5), 132.9, 128.5(2), 128.4(8), 127.9, 127.1, 127.0, 126.3, 120.8, 56.9, 50.4, 49.4. **IR** (neat) 3028, 1773, 1632, 1603, 1495 1452, 1355, 1250, 1026, 914, 731, 696 cm^{-1}. **HRMS** (ESI) m/z 236.1443 [calculated mass for $C_{17}H_{18}N$ ($M+H^+$) 236.1439].

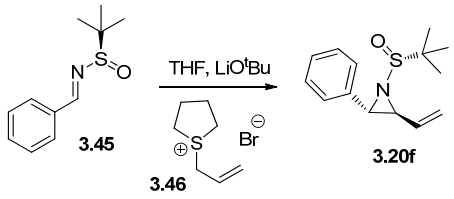


3.20i 3.20e

tert-Butyl 2-phenyl-3-vinylaziridine-1-carboxylate (**3.20e**):

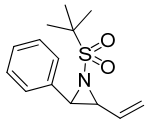
To a solution of aziridine **3.20i** (0.040 mmol, in CH_2Cl_2 and THF as described below) was added Di-tert-butyl dicarbonate (17.5 mg, 0.080 mmol, 2 equiv.). Lastly, triethylamine (8.4 mg, 0.083 mmol, 1 equiv.) was added and the reaction was stirred for 8 hours at room temperature. The reaction is concentrated and then purified by chromatography on silica gel to yield aziridine **3.20e** (3.0 mg, 37%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.27 (m, 5H), 5.55 – 5.40 (m, 2H), 5.37 – 5.33 (m, 1H), 3.46 (d, *J* = 3.0, 1H), 3.10 (dd, *J* = 8.0, 3.0, 1H), 1.45 (d, *J* = 15.1, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.2, 136.6, 133.6, 128.7, 128.0, 126.6, 120.4, 81.8, 49.7, 45.9, 28.2. **IR** (neat) 2979, 1807, 1717, 1458, 1386, 1317, 1154, 1067, 920, 865, 749, 698 cm^{-1}.



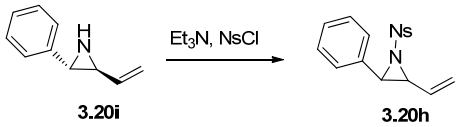
1-(tert-Butylsulfinyl)-2-phenyl-3-vinylaziridine (**3.20f**): Compound prepared according to literature procedure and matched existing characterization data.[9]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 1H), 6.34 – 6.21 (m, 0H), 5.46 (dd, *J* = 17.0, 0.7, 0H), 5.35 (dd, *J* = 10.2, 0.7, 0H), 3.54 (d, *J* = 3.6, 0H), 3.16 (dd, *J* = 9.4, 3.6, 0H), 1.28 (s, 2H). **HRMS** (ESI) m/z 250.1260 [calculated mass for $C_{14}H_{20}NOS$ ($M+H^+$) 250.1266].



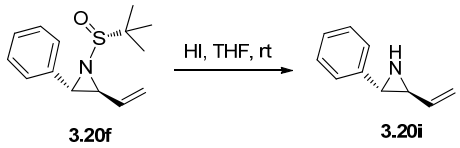
1-(tert-Butylsulfonyl)-2-phenyl-3-vinylaziridine (**3.20g**):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.31 (m, 3H), 7.30 – 7.24 (m, 2H), 6.18 (dt, *J* = 17.0, 10.0, 1H), 5.58 (d, *J* = 17.0, 1H), 5.45 (d, *J* = 10.3, 1H), 3.82 (d, *J* = 3.9, 1H), 3.29 (dd, *J* = 9.8, 3.9, 1H), 1.41 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.4, 131.6, 129.1, 128.7, 126.4, 122.4, 60.5, 54.1, 49.8, 24.2. **IR** (neat) 2980, 2929, 1608, 1457, 1395, 1306, 1197, 1130, 1071, 890 cm^{-1}. **HRMS** (ESI) m/z 288.1038 [calculated mass for $C_{14}H_{19}NO_2SNa$ ($M+Na^+$) 288.1034].



1-((4-Nitrophenyl)sulfonyl)-2-phenyl-3-vinylaziridine (**3.20h**):

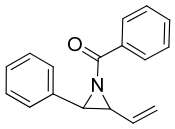
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.6, 2H), 8.14 (d, *J* = 8.6, 2H), 7.29 (s, 3H), 7.17 (s, 2H), 6.33 – 6.21 (m, 1H), 5.64 (d, *J* = 17.0, 1H), 5.55 (d, *J* = 10.3, 1H), 4.12 (d, *J* = 4.1, 1H), 3.43 (dd, *J* = 9.7, 3.9, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 150.6, 145.7, 134.2, 130.7, 129.0(3), 128.9(5), 128.9(1), 126.4, 124.5, 124.0, 56.0, 49.7. **IR** (neat) 1531, 1347, 1310, 1163, 1087, 891, 853, 745, 687, 624cm^{-1}.



3.20f 3.20i

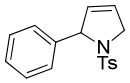
2-Phenyl-3-vinylaziridine (**3.20i**): To a stirred solution of N-sulfinylaziridine **3.20f** (0.010 g, 0.040 mmol, 1 equiv.) in THF (0.4 mL, 0.1 M) was added dropwise concentrated HI (0.070 mL, 0.115 g, 0.51 mmol, 12.8 equiv., 55%). The solution was stirred for 5 minutes when the starting material had reacted as judged by TLC. The reaction was cooled to 0°C and then quenched with a KOH solution (0.060 g, 1.1 mmol, 27 equiv.) and then warmed to room temperature. The biphasic solution is stirred for 45 minutes and then extracted with CH_2Cl_2 three times. The organic phase is dried and then concentrated. Note: in our hands aziridine (**3.20i**) was extremely unstable when neat. It appears to be quite stable to base and acid but polymerizes when concentrated to dryness. Full characterization data has been reported for this compound.[10]

^{1}H NMR (500 MHz, c_6d_6) δ 7.14 – 7.01 (m, 5H), 5.19 – 5.11 (m, 1H), 5.06 (dd, *J* = 17.0, 1.6, 1H), 4.93 (dd, *J* = 10.0, 1.5, 1H), 2.53 (d, *J* = 2.8, 1H), 2.27 (dd, *J* = 7.8, 2.8, 1H).



10j

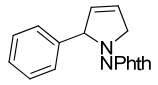
^{1}H NMR (600 MHz, $CDCl_3$) δ 8.01 (dd, *J* = 8.1, 1.0, 2H), 7.52 (t, *J* = 7.4, 1H), 7.41 (t, *J* = 7.8, 2H), 7.39 – 7.34 (m, 4H), 7.33 – 7.29 (m, 1H), 5.45 (d, *J* = 16.9, 1H), 5.33 (ddd, *J* = 16.9, 10.0, 9.2, 1H), 5.20 (d, *J* = 10.2, 1H), 3.74 (d, *J* = 2.8, 1H), 3.37 (dd, *J* = 9.0, 2.8, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 176.8, 136.8, 133.8, 133.4, 132.9, 129.4, 128.9, 128.5, 128.1, 126.5, 120.7, 52.2, 45.4. **IR** (neat) 2916, 1667, 1599, 1448, 1318, 1272, 1055, 918, 723, 694 cm^{-1}.



2-Phenyl-1-tosyl-2,5-dihydro-1H-pyrrole (**3.21a**):

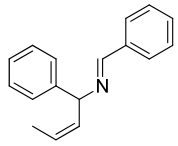
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, *J* = 8.3, 2H), 7.31 – 7.22 (m, 5H), 7.19 (d, *J* = 7.9, 2H), 5.79 (dq, *J* = 6.1, 2.0, 1H), 5.65 (dq, *J* = 6.3, 2.2, 1H), 5.52 (td, *J* = 4.6, 2.2, 1H), 4.35 (ddd, *J* = 14.6, 4.8, 2.3, 1H), 4.26 (ddt, *J* = 14.5, 5.6, 2.0, 1H), 2.38 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.3, 140.6, 135.7, 130.8, 129.7, 128.7, 128.0, 127.5, 127.4, 124.7, 70.4, 55.6, 21.7. **IR** (neat) 3030, 2867, 1597, 1493, 1455, 1345, 1162,

1092, 1057, 831, 815, 666, 596, 547 cm^{-1}. **HRMS** (ESI) m/z 300.1055 [calculated mass for $C_{17}H_{18}NO_2S$ ($M+H^+$) 300.1058].



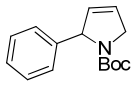
2-Phenyl-N-phthalimido-2,5-dihydro-1H-pyrrole (**3.21b**):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (dd, *J* = 5.5, 3.1, 2H), 7.70 (dd, *J* = 5.5, 3.1, 2H), 7.49 (d, *J* = 7.3, 2H), 7.32 (t, *J* = 7.4, 2H), 7.27 – 7.20 (m, 1H), 5.96 (ddd, *J* = 6.5, 4.2, 2.2, 1H), 5.86 – 5.81 (m, 1H), 5.70 – 5.63 (m, 1H), 4.40 – 4.33 (m, 1H), 4.30 – 4.22 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 167.4, 141.3, 134.4, 131.9, 130.4, 128.6, 127.8, 127.6, 126.1, 123.5, 72.7, 59.5. **IR** (neat) 3205, 1721, 1467, 1378, 1306, 1203, 1118, 1053, 883, 713, 662 cm^{-1}. **HRMS** (ESI) m/z 291.1125 [calculated mass for $C_{18}H_{15}N_2O_2$ ($M+H^+$) 291.1134].



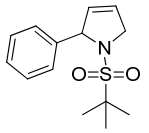
(Z)-N-Benzylidene-1-phenylbut-2-en-1-amine:

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1H), 7.81 (dd, *J* = 6.6, 3.1, 2H), 7.48 – 7.20 (m, 8H), 5.83 (ddd, *J* = 10.7, 8.9, 1.7, 1H), 5.77 – 5.62 (m, 1H), 5.40 (d, *J* = 8.8, 1H), 1.83 (d, *J* = 1.7, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 161.0, 143.6, 136.6, 132.5, 130.9, 128.8, 128.7, 128.6, 127.2, 127.1, 125.3, 70.2, 13.7.



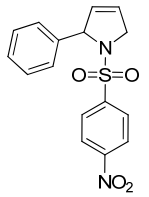
tert-Butyl-2-phenyl-2,5-dihydro-1H-pyrrole-1-carboxylate (**3.21e**): Exists as an interconverting mixture on the NMR timescale of rotamers about the carbamate bond (2.4:1@21°C in $CDCl_3$). Compound previously characterized.[11]

Major: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.33 – 7.17 (m, 5H), 5.90 (dd, *J* = 6.2, 1.8, 1H), 5.73 (dd, *J* = 6.2, 2.0, 1H), 5.37 (s, 1H), 4.37 – 4.33 (m, 2H), 1.21 (s, 9H).
Minor: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.36 – 7.15 (m, 5H), 5.85 (d, *J* = 6.3, 1H), 5.80 – 5.74 (m, 1H), 5.52 (s, 1H), 4.32 – 4.26 (m, 2H), 1.43 (s, 9H).
HRMS (ESI) m/z 246.1492 [calculated mass for $C_{15}H_{20}NO_2$ ($M+H^+$) 246.1494].



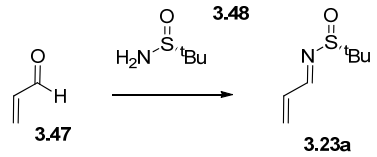
1-(tert-Butylsulfonyl)-2-phenyl-2,5-dihydro-1H-pyrrole (**3.21g**):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.23 (m, 5H), 5.93 (dq, *J* = 6.2, 2.0, 1H), 5.87 (dq, *J* = 6.1, 2.1, 1H), 5.76 (dq, *J* = 6.8, 2.3, 1H), 4.72 (dq, *J* = 14.4, 2.2, 1H), 4.15 (ddt, *J* = 14.4, 5.6, 2.1, 1H), 1.07 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 141.7, 130.2, 128.7, 128.2(6), 128.2(5), 125.1, 70.8, 60.9, 57.6, 24.3. **IR** (neat) 2976, 1455, 1312, 1130, 1105, 1041, 986, 858, 760, 680 cm^{-1}. **HRMS** (ESI) m/z 266.1204 [calculated mass for $C_{14}H_{20}NO_2S$ ($M+H^+$) 266.1215].



1-((4-Nitrophenyl)sulfonyl)-2-phenyl-2,5-dihydro-1H-pyrrole (**3.21h**):

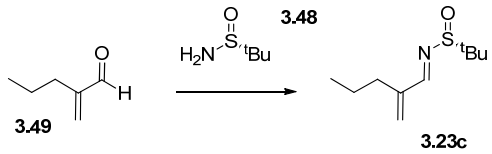
^{1}H NMR (400 MHz, CDC_3) δ 8.10 (d, *J* = 8.6, 2H), 7.55 (d, *J* = 8.6, 2H), 7.29 – 7.18 (m, 3H), 7.12 (d, *J* = 7.3, 2H), 5.94 – 5.89 (m, 1H), 5.75 – 5.70 (m, 1H), 5.63 (d, *J* = 2.8, 1H), 4.51 (d, *J* = 14.1, 1H), 4.29 – 4.21 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.7, 145.3, 139.0, 130.6, 128.8, 128.6, 128.1, 128.0, 124.7, 124.0, 70.6, 55.5. **IR** (neat) 3104, 2867, 1605, 1527, 1349, 1167, 1110, 852, 737, 625 cm^{-1}. **HRMS** (ESI) m/z 331.0742 [calculated mass for $C_{16}H_{15}N_2O_4S$ ($M+H^+$) 331.0753].



(S)-(+)-t-Butylsulfimine **3.23a**: To a solution of acrolein (2 mL, 30.50 mmol, 1.10 equiv) in THF (110 mL) was added $Ti(OEt)_4$ (33-35% soln, 36 mL, 58.48 mmol, 2.10 equiv). The reaction mixture was stirred a room temperature for 15 min and then (S)-(-)-t-butylsulfinamide (3.3707 g, 27.81 mmol, 1 equiv) was added. The reaction mixture was stirred at room temperature overnight and then it was quenched by adding brine (30 mL). The resulting slurry was filtered through a pad of celite and rinsed with EtOAc (400 mL). The filtrate was washed with brine (100 mL) and the aqueous washing was extracted with EtOAc (100 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The resultant yellow oil was

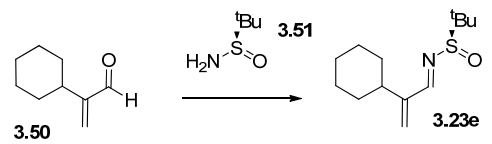
chromatographed on silica gel employing 4:1 hexanes:EtOAc as eluent to furnish **3.23a** (1.7367 g, 36% yield) as a yellow oil.

$[\alpha]_D^{21}$ +531.23° (*c* 0.46, $CHCl_3$); **FTIR** (thin film/KCl) 2978, 2961, 2926, 2903, 2869, 1625, 1577, 1474, 1458, 1390, 1363, 1324, 1185, 1085, 1003, 946, 719, 580, 563, 483, 464, 427, 405 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.22 (d, *J* = 9.3 Hz, 1H), 6.75 – 6.62 (m, 1H), 6.03 – 6.02 (m, 1H), 5.99 – 5.97 (m, 1H), 1.21 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.3, 134.7, 131.7, 57.45, 22.5; **HRMS** (ESI) *m/z* 160.0789 [calcd for $C_7H_{14}NOS$ (M+H) 160.0796].



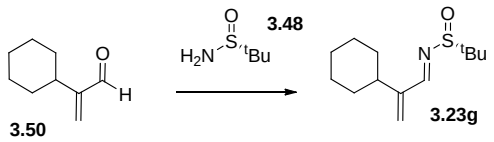
(S)-(+)-t-Butylsulfimine **3.23c**: To a solution of 2-methylenepentenal (1.5079 g, 15.37 mmol, 1.10 equiv) in THF (56 mL) was added $Ti(OEt)_4$ (33-35% soln, 17.5 mL, 28.43 mmol, 2.03 equiv) followed by (S)-(-)-t-butylsulfinamide (1.6967 g, 14 mmol, 1 equiv) was added. The reaction mixture was stirred at room temperature for 5.5 h and then it was diluted with EtOAc (56 mL) and quenched by adding brine (15 mL). The resulting slurry was filtered through a pad of celite and rinsed with EtOAc (500 mL). The filtrate was washed with brine (100 mL) and the aqueous washing was extracted with EtOAc (100 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The resultant yellow oil was chromatographed on silica gel employing 9:1 hexanes:EtOAc as eluent to furnish **3.23c** (488.4 mg, 16% yield) as a yellowish oil.

$[\alpha]_D^{21}$ +278.11° (*c* 0.47, $CHCl_3$); FTIR (thin film/KCl) 2959, 2931, 2873, 1734, 1699, 1653, 1634, 1623, 1580, 1560, 1542, 1521, 1507, 1488, 1473, 1458, 1420, 1389, 1379, 1363, 1335, 1323, 1257, 1249, 1227, 1178, 1087, 1016, 987, 924, 791, 752, 742, 611, 601, 575, 545, 524, 519, 508, 499, 472, 444, 426, 419, 403 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.13 (s, 1H), 5.75-5.73 (m, 1H), 5.68 (s, H), 2.41 – 2.20 (m, 2H), 1.59 – 1.42 (m, 2H), 1.16 (s, 9H), 0.88 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.2, 146.1, 128.8, 57.4, 32.5, 22.6, 21.3, 13.9; **HRMS** (ESI) *m/z* 202.1256 [calcd for $C_{10}H_{20}NOS$ (M+H) 202.1266].



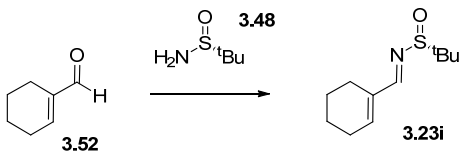
(R)-(-)-t-Butylsulfimine **3.23e**: To a solution of 2-cyclohexyl-hex-5-enal (365.8 mg, 2.65 mmol, 1.08 equiv) in THF (10 mL) was added $Ti(OEt)_4$ (33-35% soln, 3.5 mL,

5.69 mmol, 2.15 equiv) followed by (R)-(+)-t-butylsulfinamide (297.1 mg, 2.45 mmol, 1 equiv) was added. The reaction mixture was stirred at room temperature overnight and then it was diluted with EtOAc (10 mL) and quenched by adding brine (3 mL). The resulting slurry was filtered through a pad of celite and rinsed with EtOAc (100 mL). The filtrate was washed with brine (100 mL) and the aqueous washing was extracted with EtOAc (50 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The resultant yellow oil was chromatographed on silica gel employing 85:15 hexanes:EtOAc as eluent to furnish **3.23e** (473.5 mg, 74% yield) as a yellowish oil. Spectroscopic data for this material was identical to that for its enantiomer **3.23g**;



(S)-(+)-t-Butylsulfimine **3.23g:** To a solution of 2-cyclohexyl-hex-5-enal (2.0991 g, 15.19 mmol, 1.10 equiv) in THF (55 mL) was added $Ti(OEt)_4$ (33-35% soln, 17 mL, 27.61 mmol, 1.98 equiv) followed by (S)-(-)-t-butylsulfinamide (1.6882 g, 13.93 mmol, 1 equiv) was added. The reaction mixture was stirred at room temperature for 5.5 h and then it was diluted with EtOAc (55 mL) and quenched by adding brine (15 mL). The resulting slurry was filtered through a pad of celite and rinsed with EtOAc (500 mL). The filtrate was washed with brine (100 mL) and the aqueous washing was extracted with EtOAc (100 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The resultant yellow oil was chromatographed on silica gel employing 9:1 hexanes:EtOAc as eluent to furnish **3.23g** (2.2912 g, 68% yield) as a yellowish oil.

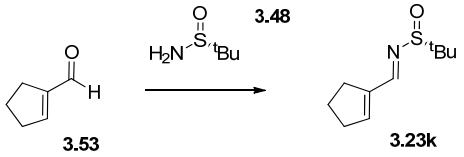
$[\alpha]_D^{21}$ +294.27° (*c* 1.05, $CHCl_3$); **FTIR** (thin film/KCl) 2980, 2927, 2853, 1619, 1581, 1475, 1460, 1450, 1390, 1363, 1343, 1324, 1266, 1227, 1179, 1135, 1088, 1053, 1031, 1017, 988, 920, 892, 787, 744, 604, 572, 530, 512, 483, 450, 413, 403 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.11 (s, 1H), 5.74 (s, 1H), 5.66 (s, 1H), 2.63 – 2.52 (m, 2H), 1.84 – 1.65 (m, 4H), 1.41 – 1.07 (m, 6H), 1.19 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.2, 151.6, 127.1, 57.5, 38.3, 33.0, 32.0, 26.8, 26.8, 26.5, 22.7; **HRMS** (ESI) *m/z* 242.1567 [calcd for $C_{13}H_{24}NOS$ (M+H) 242.1579].



(S)-(+)-t-Butylsulfimine **3.23i:** To a solution of 1-cyclohexene-1-carboxaldehyde (1.7 mL, 14.91 mmol, 1.10 equiv) in THF (55 mL) was added $Ti(OEt)_4$ (33-35% soln, 17

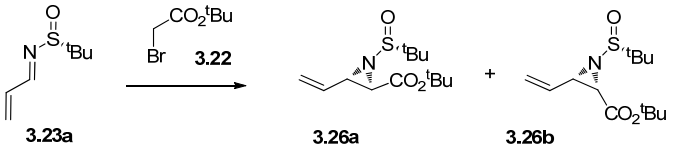
mL, 27.61 mmol, 2.03 equiv) followed by (S)-(-)-t-butylsulfinamide (1.6485 g, 13.60 mmol, 1 equiv) was added. The reaction mixture was stirred at room temperature overnight and then it was diluted with EtOAc (55 mL) and quenched by adding brine (15 mL). The resulting slurry was filtered through a pad of celite and rinsed with EtOAc (500 mL). The filtrate was washed with brine (100 mL) and the aqueous washing was extracted with EtOAc (100 mL). The combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. The resultant yellow oil was chromatographed on silica gel employing 8:2 hexanes:EtOAc as eluent to furnish **3.23i** (2.6530 g, 83% yield) as a yellow oil.

$[\alpha]_D^{21}$ +351.65° (*c* 1.41, $CHCl_3$); **FTIR** (thin film/KCl) 2978, 2931, 2865, 2843, 2825, 1634, 1581, 1474, 1456, 1434, 1389, 1362, 1335, 1303, 1267, 1229, 1191, 1136, 1086, 1045, 1016, 986, 928, 839, 794, 785, 741, 669, 586, 549, 507, 485, 464, 447, 434, 408 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.11 (s, 1H), 6.53 – 6.50 (m, 1H), 2.35 – 2.25 (m, 4H), 1.73 – 1.63 (m, 4H), 1.19 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.0, 144.6, 137.1, 56.9, 26.4, 23.3, 22.4, 22.0, 21.7; HRMS (ESI) *m/z* 214.1260 [calcd for $C_{11}H_{20}NOS$ (M+H) 214.1266].



(S)-(+)-t-Butylsulfimine **3.23k:** To a solution of 2-cyclopentene-1-carboxaldehyde (2.0115 g, 20.93 mmol, 1.10 equiv) in THF (75 mL) was added $Ti(OEt)_4$ (33-35% soln, 24 mL, 38.99 mmol, 2.05 equiv) followed by (S)-(-)-t- butylsulfinamide (2.3075 g, 19.04 mmol, 1 equiv) was added. The reaction mixture was stirred at room temperature for 5 h and then it was diluted with EtOAc (73 mL) and quenched by adding brine (20 mL). The resulting slurry was filtered through a pad of celite and rinsed with EtOAc (500 mL). The filtrate was concentrated in vacuo. The resultant orange oil was chromatographed on silica gel employing 85:15 hexanes:EtOAc as eluent to furnish **3.23k** (2.9046 g, 77% yield) as a yellow oil.

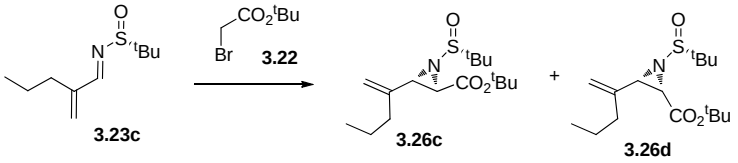
$[\alpha]_D^{21}$ +327.24° (*c* 2.07, $CHCl_3$); **FTIR** (thin film/KCl) 3134, 3045, 2957, 2926, 2901, 2870, 2841, 1695, 1619, 1574, 1507, 1474, 1456, 1443, 1390, 1362, 1338, 1297, 1257, 1227, 1181, 1167, 1130, 1085, 1039, 1018, 984, 954, 921, 906, 889, 822, 793, 754, 687, 646, 625, 584, 532, 506, 499, 476, 458 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 8.41 (s, 1H), 6.53 (dd, *J* = 4.1, 2.6 Hz, 1H), 2.64 – 2.52 (m, 4H), 2.05 – 1.92 (m, 2H), 1.19 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 159.0, 145.7, 142.6, 56.6, 33.4, 29.9, 22.5, 22.0; **HRMS** (ESI) *m/z* 200.1117 [calcd for $C_{13}H_{24}NOS$ (M+H) 200.1109].



anti Aziridine **3.26a** and *syn aziridine* **3.26b:** (S)-(+)-t-Butylsulfimine **3.23a** (656.1 mg, 4.12 mmol, 1 equiv) was taken in CH_3CN (1 mL) and concentrated under high vacuum in order to azeotropically remove water. Then it was dissolved in THF (25 mL) and cooled to -78 ºC. t-Butylbromoacetate (1.9 mL, 12.86 mmol, 3.12 equiv) was added and the reaction mixture was stirred at -78 ºC for 15 min. LHMDS (1.0 M soln in THF, 8.5 mL, 8.5 mmol, 2.06 equiv) was added ad the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was worked-up by diluting with EtOAc (100 mL) and washing with brine (2 X 50 mL). The aqueous washings were extracted with EtOAc (2 X 100 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo to a yellow oil. Silica gel chromatography employing 9:1 hexanes:EtOAc as eluent furnished two products: **3.26a** (165 mg, 15% yield, eluted second) as a yellow oil and **3.26b** (916.3 mg, 81% yield, eluted first) as a yellow oil.

3.26a: $\mathbf{[\alpha]_D^{21}}$ +122.24° (*c* 0.26, $CHCl_3$); **FTIR** (thin film/KCl) 2980, 2931, 2908, 2871, 1728, 1477, 1462, 1452, 1442, 1435, 1392, 1368, 1332, 1310, 1230, 1155, 1105, 1086, 985, 921, 894, 835, 794, 778, 746, 725, 618, 588, 562, 467 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.82 (ddd, *J* = 17.2, 10.1, 8.9 Hz, 1H), 5.46 (d, *J* = 16.7 Hz, 1H), 5.31 (d, *J* = 10.7 Hz, 1H), 3.31 (dd, *J* = 8.8, 3.3 Hz, 1H), 3.00 (d, *J* = 3.4 Hz, 1H), 1.48 (s, 9H), 1.24 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.2, 133.0, 121.2, 83.1, 57.4, 48.4, 42.0, 28.1, 22.6; **HRMS** (ESI) *m/z* 274.1472 [calcd for $C_{13}H_{24}NO_3S$ (M+H) 274.1177].

3.26b: $\mathbf{[\alpha]_D^{21}}$ +76.92° (*c* 0.47, $CHCl_3$); **FTIR** (thin film/KCl) 3088, 2980, 2934, 2907, 2872, 1739, 1728, 1641, 1477, 1460, 1392, 1368, 1332, 1300, 1277, 1254, 1220, 1153, 1084, 1051, 1037, 1019, 993, 974, 937, 883, 842, 793, 773, 738, 688, 593, 575, 550, 469, 460, 433, 412 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.79 5.49 (dd, *J* = 17.3, 1.0 Hz, 1H), 5.33 (dd, *J* = 10.4, 0.9 Hz, 1H), 3.38 (d, *J* = 7.2 Hz, 1H), 2.90 (t, *J* = 7.6 Hz, 1H), 1.46 (s, 9H), 1.25 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.1, 131.3, 121.0, 82.3, 57.6, 39.8, 35.1, 28.1, 22.6; **HRMS** (ESI) *m/z* 274.1476 [calcd for $C_{13}H_{24}NO_3S$ (M+H) 274.1177].

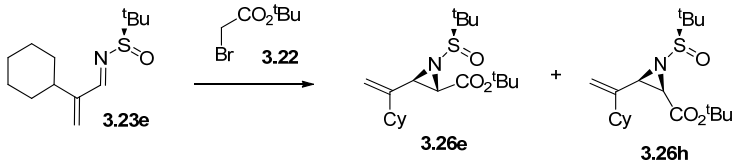


anti Aziridine **3.26c** and *syn aziridine* **3.26d:** (S)-(+)-t-Butylsulfimine **3.23c** (405.3 mg, 2.01 mmol, 1 equiv) was taken in CH_3CN (1 mL) and concentrated under high vacuum in order to azeotropically remove water. Then it was dissolved in THF (12

mL) and cooled to -78 ºC. t-Butylbromoacetate (0.9 mL, 6.01 mmol, 3.03 equiv) was added and the reaction mixture was stirred at -78 ºC for 15 min. LHMDS (1.0 M soln in THF, 4 mL, 4 mmol, 1.99 equiv) was added ad the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was worked-up by diluting with EtOAc (100 mL) and washing with brine (2 X 50 mL). The aqueous washings were extracted with EtOAc (2 X 100 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo to a brown oil. Silica gel chromatography employing 9:1 hexanes:EtOAc as eluent furnished two products: **3.26c**(154.7 mg, 24% yield, eluted second) as a yellow oil and **3.26d** (251.2 mg, 40% yield, eluted first) as a yellow solid.

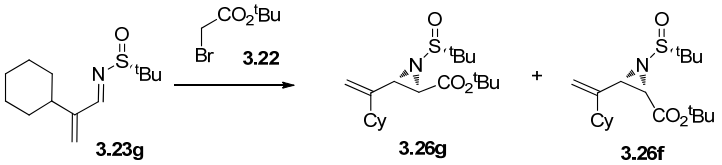
3.26c: $[\alpha]_D^{21}$ +111.58° (*c* 0.13, $CHCl_3$); **FTIR** (thin film/KCl) 2976, 2960, 2931, 2908, 2872, 1730, 1475, 1458, 1392, 1367, 1338, 1321, 1302, 1250, 1219, 1155, 1105, 987, 904, 883, 879, 852, 837, 820, 796, 721, 590 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.14 (s, 1H), 5.00 (d, *J* = 1.2 Hz, 1H), 3.29 (d, *J* = 3.4 Hz, 1H), 2.94 (d, *J* = 3.5 Hz, 1H), 1.99 – 1.84 (m, 2H), 1.51 (s, 9H), 1.51 – 1.42 (m, 2H), 1.23 (s, 9H), 0.90 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 167.1, 143.1, 114.5, 83.4, 56.6, 48.6, 42.6, 34.0, 28.3, 28.2, 28.2, 22.0, 21.0, 14.0; **HRMS** (ESI) *m/z* 316.1943 [calcd for $C_{16}H_{30}NO_3S$ (M+H) 316.1946].

3.26d: $[\alpha]_D^{21}$ +48.97° (*c* 2.04, $CHCl_3$); **FTIR** (thin film/KCl) 3092, 3061, 2960, 2933, 2872, 1743, 1727, 1650, 1579, 1477, 1458, 1392, 1367, 1292, 1254, 1226, 1156, 1085, 1040, 1020, 985, 956, 932, 909, 880, 847, 791, 775, 731, 662, 627, 596, 571, 556, 526, 503, 472, 460, 444, 431, 412, 405 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.13 (s, 1H), 4.97 (d, *J* = 1.1 Hz, 1H), 3.40 (d, *J* = 7.4 Hz, 1H), 2.84 (d, *J* = 7.4 Hz, 1H), 2.07 (t, *J* = 7.7 Hz, 2H), 1.54 – 1.42 (m, 2H), 1.41 (s, 9H), 1.29 (s, 9H), 0.92 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.2, 140.6, 112.9, 81.6, 57.3, 39.9, 36.6, 36.0, 27.8, 22.2, 20.8, 13.7; **HRMS** (ESI) *m/z* 316.1935 [calcd for $C_{16}H_{30}NO_3S$ (M+H) 316.1946].



anti Aziridine **3.26e** and *syn aziridine* **3.26h:** (R)-(-)-t-Butylsulfimine **3.23e** (473.5 mg, 1.96 mmol, 1 equiv) was taken in CH_3CN (1 mL) and concentrated under high vacuum in order to azeotropically remove water. Then it was dissolved in THF (12 mL) and cooled to -78 ºC. t-Butylbromoacetate (0.87 mL, 5.89 mmol, 3 equiv) was added and the reaction mixture was stirred at -78 ºC for 15 min. LHMDS (1.0 M soln in THF, 4 mL, 4 mmol, 2.04 equiv) was added ad the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was worked-up by diluting with EtOAc (50 mL) and washing with brine (2 X 25 mL). The aqueous washings were extracted with EtOAc (2 X 50 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo to a yellowish oil. Silica gel

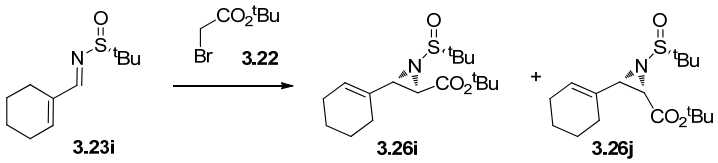
chromatography employing 9:1 hexanes:EtOAc as eluent furnished two products: **3.26e** (157.9 mg, 23% yield, eluted second) as a yellow oil and **3.26h** (331.3 mg, 48% yield, eluted first) as a yellow oil. Spectroscopic data for these materials was identical to that for their respective enantiomers: *Anti aziridine* **3.26g** and *syn aziridine* **3.26f.**



anti Aziridine **3.26g** *and syn aziridine* **3.26f***:* (S)-(+)-t-Butylsulfimine **3.23g** (131.8 mg, 0.55 mmol, 1 equiv) was taken in CH_3CN (1 mL) and concentrated under high vacuum in order to azeotropically remove water. Then it was dissolved in THF (3.3 mL) and cooled to -78 ºC. t-Butylbromoacetate (0.16 mL, 1.08 mmol, 1.99 equiv) was added and the reaction mixture was stirred at -78 ºC for 15 min. LHMDS (1.0 M soln in THF, 0.71 mL, 0.71 mmol, 1.3 equiv) was added ad the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was worked-up by diluting with EtOAc (50 mL) and washing with brine (2 X 25 mL). The aqueous washings were extracted with EtOAc (2 X 50 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo to a yellow oil. Silica gel chromatography employing 9:1 hexanes:EtOAc as eluent furnished two products: **3.26g** (53.7 mg, 28% yield, eluted second) as a colorless oil and **3.26f** (133.5 mg, 69% yield, eluted first) as a colorless oil.

3.26g: $\mathbf{[\alpha]_D^{21}}$ +151.63° (*c* 0.22, $CHCl_3$); **FTIR** (thin film/KCl) 2979, 2927, 2854, 1729, 1477, 1462, 1450, 1412, 1392, 1368, 1341, 1312, 1249, 1219, 1156, 1106, 979, 912, 905, 892, 838, 797, 745, 731, 588, 414, 404 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.03 (s, 1H), 4.92 (s, 1H), 3.23 (d, *J* = 3.4 Hz, 1H), 2.80 (d, *J* = 3.4 Hz, 1H), 1.89 (t, *J* = 11.2 Hz, 1H), 1.75- 1-65 (m, 4H), 1.50 (s, 9H), 1.22 (s, 9H), 1.29 – 1.04 (m, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.0, 148.7, 111.3, 83.4, 56.6, 47.0, 44.3, 41.7, 32.7, 32.6, 28.1, 26.7, 26.6, 26.2, 22.0; **HRMS** (ESI) *m/z* 356.2247 [calcd for $C_{19}H_{34}NO_3S$ (M+H) 356.2259].

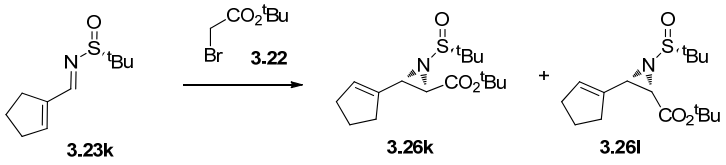
3.26f: $\mathbf{[\alpha]_D^{21}}$ +51.33° (*c* 0.46, $CHCl_3$); **FTIR** (thin film/KCl) 2978, 2932, 2926, 2854, 1741, 1727, 1643, 1478, 1451, 1425, 1392, 1367, 1351, 1293, 1250, 1226, 1192, 1156, 1084, 1038, 983, 953, 911, 891, 849, 791, 774, 730, 651, 634, 595, 564, 478, 457, 432, 422, 416, 404 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.09 (s, 1H), 4.92 (s, 1H), 3.36 (d, *J* = 7.4 Hz, 1H), 2.85 (d, *J* = 7.3 Hz, 1H), 1.97 (t, *J* = 11.2 Hz, 1H), 1.84 – 1.59 (m, 4H), 1.37 (s, 9H), 1.25 (s, 9H), 1.31 -1.02 (m, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.6, 145.8, 111.2, 82.0, 57.7, 43.0, 39.9, 36.7, 32.5, 31.7, 28.2, 26.7, 26.6, 26.3, 22.6; HRMS (ESI) *m/z* 356.2252 [calcd for $C_{19}H_{34}NO_3S$ (M+H) 356.2259].



anti Aziridine **3.26i** and *syn aziridine* **3.26j:** (S)-(+)-t-Butylsulfimine **3.23i**(738.5 mg, 3.46 mmol, 1 equiv) was taken in CH_3CN (1 mL) and concentrated under high vacuum in order to azeotropically remove water. Then it was dissolved in THF (21 mL) and cooled to -78 ºC. t-Butylbromoacetate (1.6 mL, 10.83 mmol, 3.13 equiv) was added and the reaction mixture was stirred at -78 ºC for 15 min. LHMDS (1.0 M soln in THF, 7 mL, 7 mmol, 2.02 equiv) was added ad the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was worked-up by diluting with EtOAc (100 mL) and washing with brine (2 X 50 mL). The aqueous washings were extracted with EtOAc (2 X 100 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo to a yellow oil. Silica gel chromatography employing 9:1 hexanes:EtOAc as eluent furnished two products: **3.26i** (268.8 mg, 24% yield, eluted second) as a yellow oil and **3.26j** (824.8 mg, 73% yield, eluted first) as a cream colored solid.

3.26i: $\mathbf{[\alpha]_D^{21}}$ +80.37° (*c* 1.50, $CHCl_3$); **FTIR** (thin film/KCl) 2979, 2930, 2863, 2838, 1729, 1662, 1632, 1582, 1511, 1475, 1459, 1439, 1394, 1368, 1343, 1327, 1302, 1226, 1157, 1105, 1045, 1016, 977, 929, 896, 865, 846, 789, 741, 730, 688, 675, 647, 617, 592, 562, 540, 495, 478, 462, 444, 436, 419, 404 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.78 – 5.74 (m, 1H), 3.16 (d, *J* = 3.5 Hz, 1H), 2.90 (d, *J* = 3.5 Hz, 1H), 1.93 (s, 2H), 1.83 – 1.30 (m, 6H), 1.39 (s, 9H), 1.10 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.5, 131.7, 129.2, 83.2, 56.4, 50.2, 40.4, 28.1, 25.4, 23.6, 22.4, 22.3, 21.9; **HRMS** (ESI) *m/z* 328.1936 [calcd for $C_{17}H_{30}NO_3S$ (M+H) 328.1946].

3.26j: $\mathbf{[\alpha]_D^{21}}$ +74.80° (*c* 0.48, $CHCl_3$); **FTIR** (thin film/KCl) 3091, 2981, 2936, 2878, 1744, 1643, 1481, 1459, 1438, 1396, 1370, 1316, 1281, 1226, 1157, 1132, 1046, 1035, 992, 977, 941, 890, 849, 836, 810, 791, 739, 691, 677, 626, 580, 551, 525, 472, 442, 436 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.61 (s, 1H), 3.16 (d, *J* = 7.4 Hz, 1H), 2.55 (d, *J* = 7.2 Hz, 1H), 1.80 (s, 4H), 1.46 – 1.31 (m, 4H), 1.22 (s, 9H), 1.08 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.5, 129.5, 125.2, 81.3, 57.2, 40.4, 35.8, 27.7, 26.3, 24.5, 22.19, 22.16, 22.10; **HRMS** (ESI) *m/z* 328.1938 [calcd for $C_{17}H_{30}NO_3S$ (M+H) 328.1946].

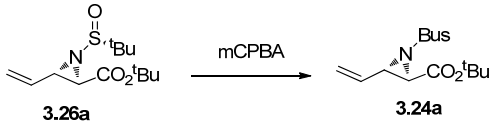


anti Aziridine **3.26k** and *syn aziridine* **3.26l:** (S)-(+)-t-Butylsulfimine **3.23k** (609,5 mg, 3.06 mmol, 1 equiv) was taken in CH_3CN (1 mL) and concentrated under high

vacuum in order to azeotropically remove water. Then it was dissolved in THF (18.5 mL) and cooled to -78 ºC. t-Butylbromoacetate (1.35 mL, 9.14 mmol, 2.99 equiv) was added and the reaction mixture was stirred at -78 ºC for 15 min. LHMDS (1.0 M soln in THF, 6.1 mL, 6.1 mmol, 2 equiv) was added ad the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was worked-up by diluting with EtOAc (100 mL) and washing with brine (2 X 50 mL). The aqueous washings were extracted with EtOAc (2 X 100 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo to a brown oil. Silica gel chromatography employing 9:1 hexanes:EtOAc as eluent furnished two products: **3.26k** (295.1 mg, 31% yield, eluted second) as a yellow oil and **3.26l** (641.0 mg, 67% yield, eluted first) as a yellow oil.

3.26k: $[\alpha]_D^{21}$ +101.98° (*c* 0.90, $CHCl_3$); **FTIR** (thin film/KCl) 2978, 2956, 2930, 2905, 2867, 2849, 1730, 1685, 1475, 1458, 1395, 1368, 1345, 1326, 1301, 1255, 1220, 1154, 1104, 1040, 1019, 974, 951, 912, 900, 876, 849, 788, 764, 743, 692, 591 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.88 – 5.84 (m, 1H), 3.51 (d, *J* = 3.5 Hz, 1H), 3.03 (d, *J* = 3.5 Hz, 1H), 2.41 – 2.33 (m, 2H), 2.31 – 2.09 (m, 2H), 1.94 – 1.82 (m, 2H), 1.51 (s, 9H), 1.22 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 167.1, 138.2, 132.3, 83.0, 56.4, 44.9, 41.4, 32.8, 31.5, 28.0, 23.0, 21.8; **HRMS** (ESI) *m/z* 314.1803 [calcd for $C_{16}H_{28}NO_3S$ (M+H) 314.1790].

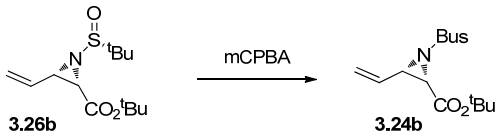
3.26l: $[\alpha]_D^{21}$ +81.87° (*c* 2.05, $CHCl_3$); **FTIR** (thin film/KCl) 3470, 3060, 3047, 2976, 2955, 2932, 2903, 2868, 2848, 2750, 2719, 2154, 1809, 1743, 1727, 1655, 1647, 1618, 1575, 1558, 1541, 1478, 1458, 1392, 1365, 1317, 1296, 1250, 1223, 1153, 1083, 1051, 1021, 958, 930, 898, 847, 793, 768, 716, 664, 644, 620, 593, 557, 506, 499, 491, 470, 455, 428, 404 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.76 – 5.73 (m, 1H), 3.40 (d, *J* = 7.4 Hz, 1H), 2.93 (d, *J* = 7.2 Hz, 1H), 2.38 – 2.26 (m, 4H), 1.93 – 1.81 (m, 2H), 1.41 (s, 9H), 1.28 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.7, 136.9, 129.7, 81.6, 57.3, 36.9, 35.9, 33.2, 32.3, 27.8, 23.3, 22.3; **HRMS** (ESI) *m/z* 314.1803 [calcd for $C_{16}H_{28}NO_3S$ (M+H) 314.1790].



3.26a **3.24a**

anti Aziridine **3.24a:** To a solution of anti aziridine **3.24a** (68.8 mg, 0.25 mmol, 1 equiv) in CH_2Cl_2 (2.5 mL) was added mCPBA (70-75%, 91.8 mg, 0.39 mmol, 1.53 equiv). The reaction mixture was stirred at room temperature for 15 min and then it was diluted with CH_2Cl_2 (25 mL) and washed with 10% aqueous $NaHSO_3$ (12.5 mL), saturated aqueous $NaHCO_3$ (12.5 mL) and brine (12.5 mL). The aqueous washings were extracted with CH_2Cl_2 (2 X 25 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. Silica gel chromatography employing 85:15 hexanes:EtOAc as eluent furnished **3.24a** (66.2 mg, 91% yield) as a yellow oil.

[α]$_D^{21}$ +2.11° (*c* 1.21, $CHCl_3$); **FTIR** (thin film/KCl) 3092, 2981, 2936, 2878, 1741, 1639, 1480, 1459, 1440, 1396, 1370, 1321, 1311, 1243, 1210, 1157, 1135, 1111, 1063, 1023, 986, 954, 907, 871, 837, 808, 777, 759, 730, 681, 657, 634, 554, 520, 501, 471, 450, 441, 431, 416, 402 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.93 (dt, *J* = 17.0, 9.8 Hz, 1H), 5.64 (dd, *J* = 16.9, 0.7 Hz, 1H), 5.46 (d, *J* = 10.2 Hz, 1H), 3.46 (dd, *J* = 9.5, 3.7 Hz, 1H), 3.33 (d, *J* = 3.7 Hz, 1H), 1.48 (s, 9H), 1.47 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.6, 130.5, 123.1, 83.0, 60.9, 48.2, 45.8, 27.9, 23.9; **HRMS** (ESI) *m/z* 290.1431 [calcd for $C_{13}H_{24}NOS$ (M+H) 290.1426].



3.26b **3.24b**

syn Aziridine **3.24b:** To a solution of syn aziridine **3.26b** (183.6 mg, 0.67 mmol, 1 equiv) in CH_2Cl_2 (6.7 mL) was added mCPBA (70-75%, 236.8 mg, 1 mmol, 1.48 equiv). The reaction mixture was stirred at room temperature for 15 min and then it was diluted with CH_2Cl_2 (25 mL) and washed with 10% aqueous $NaHSO_3$ (12.5 mL), saturated aqueous $NaHCO_3$ (12.5 mL) and brine (12.5 mL). The aqueous washings were extracted with CH_2Cl_2 (2 X 25 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. Silica gel chromatography employing 9:1 hexanes:EtOAc as eluent furnished **3.24b** (176.3 mg, 91% yield) as a colorless oil:

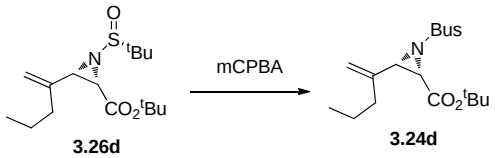
[α]$_D^{21}$ -15.70° (*c* 1.59, $CHCl_3$); **FTIR** (thin film/KCl) 3091, 2981, 2936, 2878, 1744, 1643, 1481, 1459, 1438, 1396, 1370, 1316, 1281, 1226, 1157, 1132, 1046, 1035, 992, 977, 941, 890, 849, 836, 810, 791, 739, 691, 677, 626, 580, 551, 525, 472, 442, 436 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.79 – 5.67 (m, 1H), 5.57 (dd, *J* = 17.3, 1.5 Hz, 1H), 5.41 (dd, *J* = 10.2, 1.4 Hz, 1H), 3.43 (d, *J* = 7.3 Hz, 1H), 3.39 (d, *J* = 7.4 Hz, 1H). 1.50 (s, 9H), 1.46 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.3, 129.3, 122.6, 82.8, 59.7, 44.3, 42.2, 27.9, 23.8; **HRMS** (ESI) *m/z* 312.1246 [calcd for $C_{13}H_{23}NO_4SNa$ (M+Na) 312.1245].

3.26c **3.24c**

anti Aziridine **3.24c:** To a solution of anti aziridine **3.26c** (99.4 mg, 0.32 mmol, 1 equiv) in CH_2Cl_2 (3.2 mL) was added mCPBA (70-75%, 114.9 mg, 0.48 mmol, 1.53 equiv). The reaction mixture was stirred at room temperature for 15 min and then it was diluted with CH_2Cl_2 (25 mL) and washed with 10% aqueous $NaHSO_3$ (12.5 mL), saturated aqueous $NaHCO_3$ (12.5 mL) and brine (12.5 mL). The aqueous washings were extracted with CH_2Cl_2 (2 X 25 mL) and the combined organic phases were dried

over $MgSO_4$, filtered and concentrated in vacuo. Silica gel chromatography employing 9:1 hexanes:EtOAc as eluent furnished **3.24c** (78.8 mg, 75% yield) as a colorless oil.

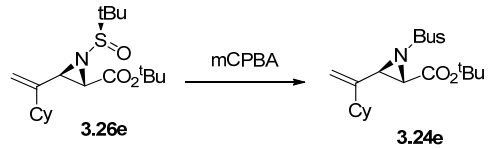
$[\alpha]_D^{21}$ +27.23° (*c* 0.08, $CHCl_3$); **FTIR** (thin film/KCl) 2978, 2962, 2935, 2875, 1741, 1645, 1481, 1456, 1394, 1369, 1323, 1257, 1254, 1250, 1223, 1159, 1132, 1113, 1097, 1059, 1039, 1020, 989, 970, 930, 926, 922, 879, 864, 858, 839, 808, 756, 733, 685, 654, 644, 640, 621, 596, 557, 544, 538, 534, 515, 496, 471, 453, 436, 415, 409, 403 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.21 (s, 1H), 5.07 (d, *J* = 1.0 Hz, 1H), 3.72 (d, *J* = 3.8 Hz, 1H), 3.14 (d, *J* = 3.8 Hz, 1H), 2.06 – 1.93 (m, 2H), 1.51 (s, 9H), 1.55 – 1.39 (m, 2H), 1.45 (s, 9H), 0.93 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (100 MHz, $CDCl_3$) δ 165.3, 142.0, 115.3, 83.4, 61.0, 49.0, 46.2, 34.5, 28.0, 24.2, 21.0, 14.0; **HRMS** (ESI) *m/z* 332.1891 [calcd for $C_{16}H_{30}NO_4S$ (M+H) 332.1896].



3.26d **3.24d**

syn Aziridine **3.24d:** To a solution of syn aziridine **3.26d** (204 mg, 0.65 mmol, 1 equiv) in CH_2Cl_2 (6.5 mL) was added mCPBA (70-75%, 235.3 mg, 0.99 mmol, 1.53 equiv). The reaction mixture was stirred at room temperature for 15 min and then it was diluted with CH_2Cl_2 (25 mL) and washed with 10% aqueous $NaHSO_3$ (12.5 mL), saturated aqueous $NaHCO_3$ (12.5 mL) and brine (12.5 mL). The aqueous washings were extracted with CH_2Cl_2 (2 X 25 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. Silica gel chromatography employing 9:5 hexanes:EtOAc as eluent furnished **3.24d** (182.5 mg, 85% yield) as a colorless oil.

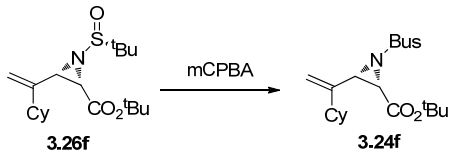
$[\alpha]_D^{21}$ +8.69° (*c* 0.95, $CHCl_3$); **FTIR** (thin film/KCl) 3095, 2978, 2965, 2935, 2875, 1746, 1731, 1651, 1579, 1481, 1459, 1432, 1395, 1369, 1315, 1230, 1190, 1157, 1133, 1058, 1040, 987, 957, 914, 881, 849, 838, 810, 792, 734, 688, 678, 644, 603, 558, 518, 484, 465, 437, 408, 402 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.18 (s, 1H), 5.01 (d, *J* = 1.3 Hz, 1H), 3.45 (d, *J* = 7.6 Hz, 1H), 3.38 (d, *J* = 7.6 Hz, 1H), 2.09 (t, *J* = 7.7 Hz, 2H), 1.54 (s, 9H), 1.51 – 1.45 (m, 2H), 1.42 (s, 9H), 0.93 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.9, 139.5, 113.8, 82.7, 60.1, 45.1, 43.7, 36.6, 28.1, 24.0, 20.9, 14.0; **HRMS** (ESI) *m/z* 290.1431 [calcd for 332.1888 [calcd for $C_{16}H_{30}NO_4S$ (M+H) 332.1896].



3.26e **3.24e**

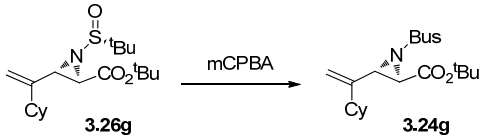
anti Aziridine **3.24e:** To a solution of anti aziridine **3.26e** (157.9 mg, 0.44 mmol, 1 equiv) in CH_2Cl_2 (4.5 mL) was added mCPBA (70-75%, 158 mg, 0.66 mmol, 1.5

equiv). The reaction mixture was stirred at room temperature for 2.5 h and then it was diluted with CH_2Cl_2 (25 mL) and washed with concentrated aqueous $NaHSO_3$ (12.5 mL), saturated aqueous $NaHCO_3$ (12.5 mL) and brine (12.5 mL). The aqueous washings were extracted with CH_2Cl_2 (2 X 25 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. Silica gel chromatography employing 9:1 hexanes:EtOAc as eluent furnished **3.24e** (101.8 mg, 62% yield) as a white solid. Spectroscopic data for this material was identical to that for its enantiomer **3.24g**;



3.26f **3.24f**

syn Aziridine **3.24f:** To a solution of anti aziridine **3.26f** (245.4 mg, 0.69 mmol, 1 equiv) in CH_2Cl_2 (7 mL) was added mCPBA (70-75%, 246.6 mg, 1.04 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 15 min and then it was diluted with CH_2Cl_2 (25 mL) and washed with 20% $NaHSO_3$ (12.5 mL), saturated aqueous $NaHCO_3$ (12.5 mL) and brine (12.5 mL). The aqueous washings were extracted with CH_2Cl_2 (2 X 25 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. Silica gel chromatography employing 9:1 hexanes:EtOAc as eluent furnished **3.24f** (239.8 mg, 94% yield) as a yellow oil. An analytical sample (white crystals) was obtained by a second flash chromatography employing 9:1 hexanes:EtOAc as eluent.
$[\alpha]_D^{21}$ +13.83° (*c* 0.59, $CHCl_3$); **FTIR** (thin film/KCl) 2979, 2937, 2929, 2923, 2855, 1744, 1728, 1644, 1480, 1451, 1395, 1368, 1318, 1230, 1199, 1156, 1130, 1060, 1039, 984, 954, 915, 891, 849, 838, 811, 796, 777, 735, 684, 655, 600, 563, 550, 524 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.14 (s, 1H), 4.97 (s, 1H), 3.42 (d, *J* = 7.6 Hz, 1H), 3.38 (d, *J* = 7.7 Hz, 1H), 2.05 – 1.91 (m, 1H), 1.87 – 1.61 (m, 4H), 1.50 (s, 9H), 1.39 (s, 9H), 1.33 – 0.99 (m, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 163.8, 144.3, 111.9, 82.6, 60.1, 45.2, 43.8, 42.9, 32.4, 31.7, 28.2, 26.7, 26.5, 26.3, 24.0; **HRMS** (ESI) *m/z* 372.2204 [calcd for $C_{19}H_{34}NO_4S$ (M+H) 372.2209].

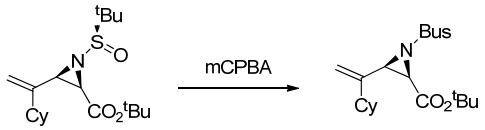


3.26g **3.24g**

anti Aziridine **3.24g:** To a solution of anti aziridine **3.26g** (46.1 mg, 0.13 mmol, 1 equiv) in CH_2Cl_2 (1.4 mL) was added mCPBA (70-75%, 49.3 mg, 0.21 mmol, 1.6 equiv). The reaction mixture was stirred at room temperature for 1 h and then it was diluted with CH_2Cl_2 (25 mL) and washed with concentrated aqueous $NaHSO_3$ (12.5 mL), saturated aqueous $NaHCO_3$ (12.5 mL) and brine (12.5 mL). The aqueous

washings were extracted with CH_2Cl_2 (2 X 25 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. Silica gel chromatography employing 9:1 hexanes:EtOAc as eluent furnished **3.24g** (36.4 mg, 76% yield) as a yellowish oil. An analytical sample (white needles) was obtained by a second flash chromatography employing 9:1 hexanes:EtOAc as eluent.

$[\alpha]_D^{21}$ +47.15° (*c* 0.19, $CHCl_3$); **FTIR** (thin film/KCl) 2981, 2928, 2854, 1741, 1480, 1450, 1395, 1369, 1323, 1222, 1158, 1132, 1096, 982, 967, 913, 892, 840, 808, 743, 683, 418, 403 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.05 (s, 1H), 4.98 (s, 1H), 3.68 (d, *J* = 3.8 Hz, 1H), 3.01 (d, *J* = 3.8 Hz, 1H), 1.96 (t, *J* = 11.3 Hz, 1H), 1.84 – 1.64 (m, 4H), 1.50 (s, 9H), 1.44 (s, 9H), 1.37 – 1.07 (m, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.1, 147.9, 111.6, 83.3, 60.9, 47.8, 47.6, 42.0, 32.5, 32.5, 28.0, 26.7, 26.6, 26.3, 24.2; **HRMS** (ESI) *m/z* 372.2206 [calcd for $C_{19}H_{34}NO_4S$ (M+H) 372.2209].



3.26h **3.24h**

syn Aziridine **3.24h:** To a solution of syn aziridine **3.26h** (331.3 mg, 0.93 mmol, 1 equiv) in CH_2Cl_2 (9.5 mL) was added mCPBA (70-75%, 347.7 mg, 1.46 mmol, 1.57 equiv). The reaction mixture was stirred at room temperature for 100 min and then it was diluted with CH_2Cl_2 (25 mL) and washed with concentrated aqueous $NaHSO_3$ (12.5 mL), saturated aqueous $NaHCO_3$ (12.5 mL) and brine (12.5 mL). The aqueous washings were extracted with CH_2Cl_2 (2 X 25 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. Silica gel chromatography employing 9:1 hexanes:EtOAc as eluent furnished **3.24h** (293.1 mg, 84% yield) as white needles. Spectroscopic data for this material was identical to that for its enantiomer **3.24f**.

3.26i **3.24i**

anti Aziridine **3.24i:** To a solution of anti aziridine **3.26i** (92 mg, 0.28 mmol, 1 equiv) in CH_2Cl_2 (2.8 mL) was added $NaHCO_3$ (118.6 mg, 1.41 mmol, 5.03 equiv) followed by mCPBA (70-75%, 92.3 mg, 0.39 mmol, 1.38 equiv). The reaction mixture was stirred at room temperature for 15 min and then it was diluted with CH_2Cl_2 (30 mL) and washed with 5% aqueous $NaHSO_3$ (15 mL), 1M NaOH (15 mL) and brine (15 mL). The aqueous washings were extracted with CH_2Cl_2 (2 X 30 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo.

Silica gel chromatography employing 9:1 hexanes:EtOAc as eluent furnished **3.24i** (84.8 mg, 88% yield) as a colorless oil.

$[\alpha]_D^{22}$ +24.54° (*c* 0.78, $CHCl_3$); **FTIR** (thin film/KCl) 2980, 2933, 2862, 2837, 1743, 1732, 1479, 1456, 1437, 1423, 1416, 1394, 1369, 1342, 1321, 1250, 1221, 1157, 1132, 1109, 1095, 1070, 1045, 980, 939, 908, 872, 845, 829, 808, 795, 756, 731, 700, 673, 661, 621, 607, 559, 511, 469, 430, 422, 418, 407, 403 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.00 (s, 1H), 3.69 (d, *J* = 3.8 Hz, 1H), 3.25 (d, *J* = 3.8 Hz, 1H), 2.07 (s, 2H), 1.98 – 1.77 (m, 2H), 1.73 – 1.53 (m, 4H), 1.50 (s, 9H), 1.43 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.7, 130.7, 130.2, 83.0, 60.7, 51.1, 43.7, 27.9, 25.4, 24.0, 23.9, 22.24, 22.18; **HRMS** (ESI) *m/z* 366.1712 [calcd for $C_{17}H_{29}NO_4SNa$ (M+Na) 366.1715].

3.26j **3.24j**

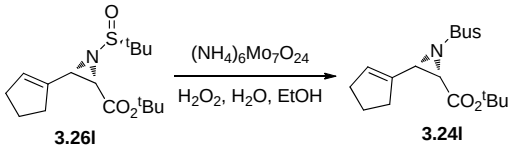
syn Aziridine **3.24j:** To a solution of syn aziridine **3.26j** (104.7 mg, 0.31 mmol, 1 equiv) in CH_2Cl_2 (3.1 mL) was added mCPBA (70-75%, 102 mg, 0.43 mmol, 1.34 equiv). The reaction mixture was stirred at room temperature for 15 min and then it was diluted with CH_2Cl_2 (50 mL) and washed with 10% aqueous $NaHSO_3$ (25 mL), saturated aqueous $NaHCO_3$ (25 mL) and brine (25 mL). The aqueous washings were extracted with CH_2Cl_2 (2 X 50 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. Silica gel chromatography employing 9:1 hexanes:EtOAc as eluent furnished **3.24j** (76.9 mg, 73% yield) as a colorless oil. An analytical sample (colorless oil) was obtained by a second flash chromatography employing 9:1 hexanes:EtOAc as eluent.

$[\alpha]_D^{21}$ +189.63° (*c* 0.85, $CHCl_3$); **FTIR** (thin film/KCl) 2979, 2931, 2889, 2880, 2861, 2838, 1747, 1729, 1481, 1459, 1440, 1395, 1368, 1341, 1316, 1229, 1157, 1130, 1077, 1046, 1033, 959, 922, 895, 846, 811, 783, 757, 732, 686, 553, 527, 515, 468, 432, 418, 412 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.81 -5-84 (m, 1H), 3.37 (d, *J* = 7.6 Hz, 1H), 3.28 (d, *J* = 7.6 Hz, 1H), 2.0 – 1.93 (m, 4H), 1.50 (s, 9H), 1.43 – 1.62 (m, 4H), 1.40 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.3, 128.6, 126.6, 82.5, 60.1, 45.1, 44.1, 28.1, 26.4, 24.8, 24.1, 22.4, 22.2; **HRMS** (ESI) *m/z* 344.1896 [calcd for $C_{17}H_{30}NO_4S$ (M+H) 344.1846], 366.1705 [calcd for $C_{17}H_{29}NO_4SNa$ (M+Na) 366.1715.

3.26k **3.24k**

anti Aziridine **3.24k:** To a solution of anti aziridine **3.26k** (49.8 mg, 0.16 mmol, 1 equiv) in CH_2Cl_2 (1.6 mL) was added mCPBA (70-75%, 91.8 mg, 0.39 mmol, 1.53 equiv). The reaction mixture was stirred at room temperature for 10 min and then it was diluted with CH_2Cl_2 (30 mL) and washed with 5% aqueous $NaHSO_3$ (15 mL), 1M NaOH (15 mL) and brine (15 mL). The aqueous washings were extracted with CH_2Cl_2 (2 X 30 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. Silica gel chromatography employing 9:1 hexanes:EtOAc as eluent furnished **3.24k** (22.5 mg, 45% yield) as a colorless oil.

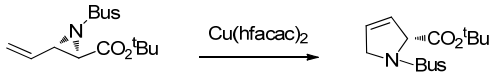
$[\alpha]_D^{21}$ +3.35° (*c* 0.44, $CHCl_3$); **FTIR** (thin film/KCl) 2980, 2958, 2933, 2872, 2848, 1741, 1479, 1458, 1417, 1414, 1394, 1369, 1321, 1250, 1221, 1155, 1132, 1105, 1092, 1041, 1024, 976, 953, 924, 839, 823, 810, 793, 771, 710, 700, 671, 553, 509 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 6.02 – 6.00 (m, 1H), 3.83 (d, *J* = 3.5 Hz, 1H), 3.33 (d, *J* = 3.7 Hz, 1H), 2.45 – 2.18 (m, 4H), 1.97 – 1.84 (m, 2H), 1.49 (s, 9H), 1.43 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.7, 136.5, 134.7, 83.1, 60.9, 46.1, 44.6, 32.9, 31.8, 27.9, 24.0, 23.3; **HRMS** (ESI) *m/z* 352.1557 [calcd for $C_{16}H_{27}NO_4SNa$ (M+Na) 352.1559].



3.26l **3.24l**

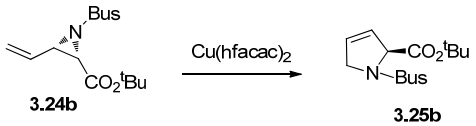
syn Aziridine **3.24l:** Ammonium molibdate tetrahydrate (40.6 mg, 3.29 X 10^{-2} mmol, 0,2 equiv) was added to an aqueous solution of H_2O_2 (30%, 0.17 mL, 1.67 mmol, 10.01 equiv) cooled to 0 ºC. The mixture was stirred at this temperature for 10 min an then a solution of syn aziridine **3.26l** (51.7 mg, 0.16 mmol, 1 equiv) in EtOH (1.5 mL) was added. The reaction mixture was stirred at room temperature for 5.5 h and then it was diluted with CH_2Cl_2 (25 mL) and washed with 10% aqueous $NaHSO_3$ (12.5 mL), saturated aqueous $NaHCO_3$ (25 mL) and brine (25 mL). The aqueous washings were extracted with CH_2Cl_2 (2 X 25 mL) and the combined organic phases were dried over $MgSO_4$, filtered and concentrated in vacuo. Silica gel chromatography employing 9:1 hexanes:EtOAc as eluent furnished **3.24l** (51.1 mg, 94% yield) as a colorless oil.

$[\alpha]_D^{21}$ +39.74° (*c* 0.53, $CHCl_3$); **FTIR** (thin film/KCl) 2979, 2935, 2873, 2850, 1747, 1732, 1481, 1458, 1395, 1368, 1317, 1251, 1227, 1156, 1130, 1050, 1023, 961, 933, 899, 857, 847, 811, 782, 733, 692, 553, 516 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.83 – 5.81 (m, 1H), 3.50 (d, *J* = 7.6 Hz, 1H), 3.44 (d, *J* = 7.6 Hz, 1H), 2.39 – 2.27 (m, 4H), 1.97 – 1.81 (m, 2H), 1.53 (s, 9H), 1.43 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 164.4, 135.6, 131.3, 82.7, 60.1, 44.6, 41.2, 33.3, 32.6, 28.1, 24.1, 23.5; **HRMS** (ESI) *m/z* 330.1753 [calcd for $C_{16}H_{28}NO_4S$ (M+H) 330.1739], 352.1545 [calcd for $C_{16}H_{27}NO_4SNa$ (M+Na) 352.1559].



3.24a 3.25a

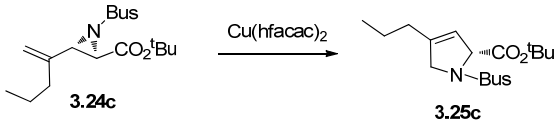
(+)-Dehydroproline **3.25a:** Aziridine **3.24a** (54.2 mg, 0.187 mmol, 1 equiv) was taken in a 5 mM solution of $Cu(hfacac)_2 \cdot H_2O$ in toluene (1.9 mL, 9.5 X 10^{-3} mmol, 0.05 equiv). The mixture was stirred in a sealed tube at 150 ºC for 5 h and then it was allowed to cool to room temperature and concentrated in vacuo The resultant brown solid was chromatographed on silica gel employing 9:1 hexanes:EtOAc as eluent to furnish **3.25a** (38.9 mg, 72% yield) as white crystals. Spectroscopic data for this material was identical to that for its enantiomer **3.25b** but with opposite optical rotation: $\mathbf{[\alpha]_D^{21}}$ +252.05° (*c* 0.39, $CHCl_3$).



3.24b 3.25b

(-)-Dehydroproline **3.25b:** Aziridine **3.24b** (76.4 mg, 0.264 mmol, 1 equiv) was taken in a 5 mM solution of $Cu(hfacac)_2 \cdot H_2O$ in toluene (2.6 mL, 1.3 X 10^{-2} mmol, 0.05 equiv). The mixture was stirred in a sealed tube at 150 ºC for 5 h and then it was allowed to cool to room temperature and concentrated in vacuo The resultant brown solid was chromatographed on silica gel employing 9:1 hexanes:EtOAc as eluent to furnish **3.25b** (59 mg, 77% yield) as white crystals.

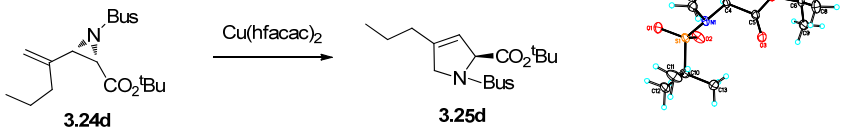
$\mathbf{[\alpha]_D^{21}}$ -215.83° (*c* 0.46, $CHCl_3$); **FTIR** (thin film/KCl) 2978, 2938, 2923, 2874, 1742, 1483, 1462, 1395, 1369, 1338, 1318, 1307, 1244, 1221, 1203, 1160, 1135, 1108, 1050, 1026, 984, 948, 927, 876, 831, 823, 791, 731, 685, 672, 588, 530, 517, 469, 414 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.99 – 5.90 (m, 1H), 5.82 – 5.73 (m, 1H), 5.23 (s, 1H), 4.56 (d, *J* = 14.4 Hz, 1H), 4.19 (d, *J* = 12.1 Hz, 1H), 1.45 (s, 9H), 1.43 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.1, 129.0, 125.6, 82.2, 69.7, 61.7, 57.4, 28.1, 24.5; **HRMS** (ESI) *m/z* 290.1423 [calcd for $C_{13}H_{24}NO_4S$ (M+H) 290.1426].



3.24c 3.25c

(+)-Dehydroproline **3.25c:** Aziridine **3.24c** (27.1 mg, 0.082 mmol, 1 equiv) was taken in a 5 mM solution of $Cu(hfacac)_2 \cdot H_2O$ in toluene (0.82 mL, 4.1 X 10^{-3} mmol, 0.05 equiv). The mixture was stirred in a sealed tube at 150 ºC for 5 h and then it was allowed to cool to room temperature and concentrated in vacuo The resultant brown oil was chromatographed on silica gel employing 9:1 hexanes:EtOAc as eluent to furnish **3.25c** (23.5 mg, 87% yield) as a yellowish oil. Spectroscopic data for this

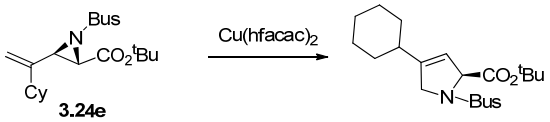
material was identical to that for its enantiomer **3.25d** but with opposite optical rotation: $[\alpha]_D^{21}$ +197.94° (*c* 0.28, $CHCl_3$)



3.24d **3.25d**

(-)-Dehydroproline **3.25d:** Aziridine **3.24d** (97.3 mg, 0.294 mmol, 1 equiv) was taken in a 5 mM solution of $Cu(hfacac)_2 \cdot H_2O$ in toluene (2.94 mL, 1.47 X 10^{-2} mmol, 0.05 equiv). The mixture was stirred in a sealed tube at 150 ºC for 5 h and then it was allowed to cool to room temperature and concentrated in vacuo The resultant brown solid was chromatographed on silica gel employing 9:1 hexanes:EtOAc as eluent to furnish **3.25d** (83.5 mg, 86% yield) as tan crystals.

$[\alpha]_D^{21}$ -197.45° (*c* 0.46, $CHCl_3$); **FTIR** (thin film/KCl) 2971, 2962, 2934, 2873, 1742, 1481, 1460, 1394, 1368, 1318, 1251, 1212, 1158, 1132, 1078, 1047, 1023, 987, 953, 918, 879, 837, 827, 808, 776, 766, 737, 681, 631, 601, 584, 569, 557, 548, 514, 503, 497, 487, 480 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.35 – 5.32 (m, 1H), 5.09 (s, 1H), 4.33 (d, *J* = 13.6 Hz, 2H), 4.08 (d, *J* = 12.2 Hz, 2H), 2.05 (t, *J* = 7.4 Hz, 2H), 1.50 – 1.40 (m, 1H), 1.41 (s, 9H), 1.38 (s, 9H), 0.88 (t, *J* = 7.3 Hz, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.5, 143.6, 118.4, 81.8, 69.9, 61.6, 59.1, 30.6, 28.0, 24.5, 20.6, 13.8; **HRMS** (ESI) *m/z* 332.1897 [calcd for $C_{16}H_{30}NO_4S$ (M+H) 332.1896].

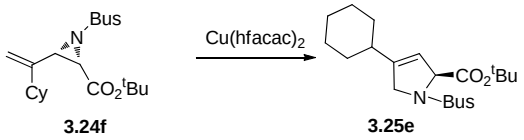


3.24e **3.25e**

(-)-Dehydroproline **3.25e:** Aziridine **3.24e** (101.8 mg, 0.274 mmol, 1 equiv) was taken in a 5 mM solution of $Cu(hfacac)_2 \cdot H_2O$ in toluene (2.74 mL, 1.37 X 10^{-2} mmol, 0.05 equiv). The mixture was stirred in a sealed tube at 150 ºC for 5 h and then it was allowed to cool to room temperature and concentrated in vacuo The resultant brown solid was chromatographed on silica gel employing 9:1 hexanes:EtOAc as eluent to furnish **3.25e** (91.2 mg, 90% yield) as a beige solid. Spectroscopic data for this material was identical to that for its enantiomer **3.25g** but with opposite optical rotation.

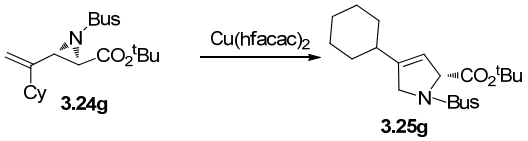
$[\alpha]_D^{21}$ -162.36° (*c* 0.71, $CHCl_3$); **FTIR** (thin film/KCl) 2978, 2928, 2855, 1742, 1655, 1481, 1451, 1394, 1368, 1319, 1254, 1233, 1212, 1158, 1134, 1054, 1022, 1005, 988, 953, 919, 891, 837, 833, 808, 781, 736, 678, 590, 513, 471cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.33 – 5.26 (m, 1H), 5.08 (bs, 1H), 4.39 (d, *J* = 13.6 Hz, 1H), 4.12 (d, *J* = 11.2 Hz, 1H), 2.03 (t, *J* = 10.3 Hz, 1H), 1.81 – 1.56 (m, 4H), 1.41 (s, 9H), 1.38 (s, 9H),

1.29 – 1.05 (m, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.6, 148.8, 116.6, 81.7, 69.9, 61.6, 57.9, 37.8, 31.8, 31.6, 28.1, 26.15, 26.11, 26.10, 24.5; **HRMS** (ESI) *m/z* 372.2205 [calcd for $C_{19}H_{34}NO_4S$ (M+H) 372.2209].



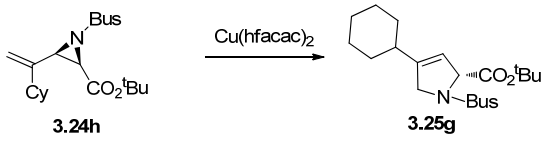
3.24f **3.25e**

(-)-Dehydroproline **3.25e:** Aziridine **3.24f** (103.4 mg, 0.278 mmol, 1 equiv) was taken in a 5 mM solution of $Cu(hfacac)_2 \cdot H_2O$ in toluene (2.8 mL, 1.4 X 10^{-2} mmol, 0.05 equiv). The mixture was stirred in a sealed tube at 150 ºC for 5 h and then it was allowed to cool to room temperature and concentrated in vacuo The resultant brown solid was chromatographed on silica gel employing 9:1 hexanes:EtOAc as eluent to furnish **3.25e** (92.6 mg, 90% yield) as a beige solid. **$[\alpha]_D^{21}$** -160.21° (*c* 0.85, $CHCl_3$).



3.24g **3.25g**

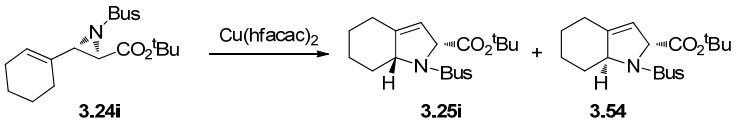
(+)-Dehydroproline **3.25g:** Aziridine **3.24g** (129.1 mg, 0.347 mmol, 1 equiv) was taken in a 5 mM solution of $Cu(hfacac)_2 \cdot H_2O$ in toluene (3.5 mL, 1.75 X 10^{-2} mmol, 0.05 equiv). The mixture was stirred in a sealed tube at 150 ºC for 5 h and then it was allowed to cool to room temperature and concentrated in vacuo The resultant brown solid was chromatographed on silica gel employing 9:1 hexanes:EtOAc as eluent to furnish **3.25g** (104.7 mg, 81% yield) as an off-white solid. Spectroscopic data for this material was identical to that for the product of the rearrangement of **3.25h**: **$[\alpha]_D^{21}$** +157.24° (*c* 1.01, $CHCl_3$).



3.24h **3.25g**

(+)-Dehydroproline **3.25g:** Aziridine **3.24h** (101.2 mg, 0.272 mmol, 1 equiv) was taken in a 5 mM solution of $Cu(hfacac)_2 \cdot H_2O$ in toluene (2.72 mL, 1.36 X 10^{-2} mmol, 0.05 equiv). The mixture was stirred in a sealed tube at 150 ºC for 5 h and then it was allowed to cool to room temperature and concentrated in vacuo The resultant brown solid was chromatographed on silica gel employing 9:1 hexanes:EtOAc as eluent to furnish **3.25g** (84.5 mg, 83% yield) as tan crystals.

$[\alpha]_D^{21}$ +165.74° (*c* 0.58, $CHCl_3$); **FTIR** (thin film/KCl) 2978, 2928, 2855, 1742, 1657, 1585, 1481, 1451, 1394, 1368, 1319, 1254, 1233, 1212, 1158, 1133, 1054, 1023, 1005, 988, 953, 920, 891, 837, 833, 808, 781, 738, 678, 590, 513, 470 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.32 – 5.26 (m, 1H), 5.09 (bs, 1H), 4.39 (d, *J* = 13.5 Hz, 1H), 4.13 (d, *J* = 10.9 Hz, 1H), 2.10 – 1.97 (m, 1H), 1.83 – 1.57 (m, 4H), 1.42 (s, 9H), 1.38 (s, 9H), 1.29 – 1.08 (m, 6H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.6, 148.8, 116.7, 81.8, 69.9, 61.7, 57.9, 37.8, 31.8, 31.7, 28.1, 26.17, 26.13, 26.12, 24.5; **HRMS** (ESI) *m/z* 372.2219 [calcd for $C_{19}H_{34}NO_4S$ (M+H) 372.2209].

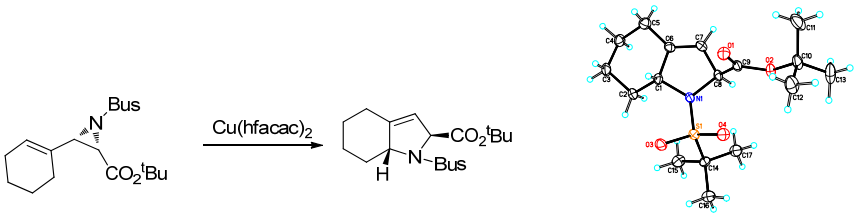


3.24i **3.25i** **3.54**

(+)-Dehydroproline **3.25i:** Aziridine **3.24i** (48.2 mg, 0.14 mmol, 1 equiv) was taken in a 5 mM solution of $Cu(hfacac)_2{\cdot}H_2O$ in toluene (1.4 mL, 7 X 10^{-3} mmol, 0.05 equiv). The mixture was stirred in a sealed tube at 150 ºC for 5 h and then it was allowed to cool to room temperature and concentrated in vacuo to a brown oil. Silica gel chromatography employing 9:1 hexanes:EtOAc as eluent furnished two products: **3.25i** (32.3 mg, 67% yield, eluted first) as a yellowish oil and **3.54** (4.9 mg, 10% yield, eluted second) as a yellowish oil.

3.25i: $[\alpha]_D^{21}$ +147.71° (*c* 0.85, $CHCl_3$); **FTIR** (thin film/KCl) 2978, 2937, 2858, 1743, 1728, 1672, 1481, 1456, 1394, 1369, 1315, 1279, 1250, 1232, 1211, 1159, 1147, 1132, 1107, 1092, 1080, 1061, 1032, 1020, 993, 966, 951, 918, 872, 858, 839, 829, 808, 779, 764, 742, 685, 658, 652, 648, 611, 582, 544, 517, 494, 465, 445, 430, 426, 407, 403 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.20 (s, 1H), 5.07 (s, 1H), 4.60 – 4.52 (m, 1H), 2.51 – 2.42 (m, 1H), 2.24 (s, 1H), 1.99 (t, *J* = 13.0 Hz, 1H), 1.76 (d, *J* = 8.2 Hz, 2H), 1.64 – 1.47 (m, 1H), 1.42 (s, 9H), 1.36 (s, 9H), 1.32 – 1.10 (m, 2H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.8, 145.5, 114.4, 81.8, 70.2, 68.8, 61.0, 36.4, 28.6, 28.0, 27.0, 24.7, 24.3; **HRMS** (ESI) *m/z* 344.1900 [calcd for $C_{17}H_{30}NO_4S$ (M+H) 344.1896]; 366.1719 [calcd for $C_{17}H_{29}NO_4SNa$ (M+Na) 366.1715].

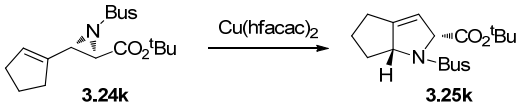
3.54:. Spectroscopic data for this material was identical to that for its enantiomer **3.25j** but with opposite optical rotation: **$[\alpha]_D^{21}$** +266.71° (*c* 0.10, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.29 (d, *J* = 2.0 Hz, 1H), 4.60 (bs, 1H), 4.53 (dd, *J* = 9.9, 4.5 Hz, 1H), 2.55 – 2.46 (m, 2H), 2.12 – 1.98 (m, 1H), 1.85 – 1.76 (m, 2H), 1.46 (s, 9H), 1.41 (s, 9H), 1.38 – 1.10 (m, 3H).



3.24j **3.25j**

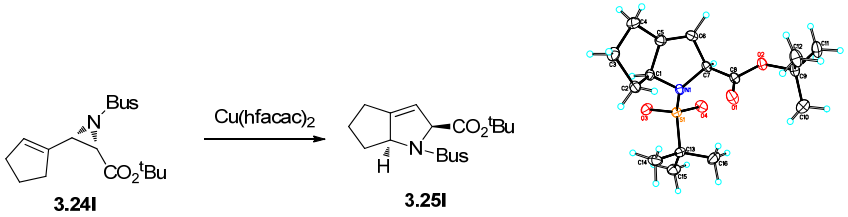
(-)-Dehydroproline **3.25j:** Aziridine **3.24j** (76.9 mg, 0.224 mmol, 1 equiv) was taken in a 5 mM solution of $Cu(hfacac)_2 \cdot H_2O$ in toluene (2.23 mL, 1.115 X 10^{-2} mmol, 0.05 equiv). The mixture was stirred in a sealed tube at 150 ºC for 5 h and then it was allowed to cool to room temperature and concentrated in vacuo The resultant brown solid was chromatographed on silica gel employing 9:1 hexanes:EtOAc as eluent to furnish **3.25j** (66.7 mg, 87% yield) as tan crystals.

$[\alpha]_D^{21}$ -281.37° (*c* 1.33, $CHCl_3$); **FTIR** (thin film/KCl) 3091, 3007, 2996, 2983, 2970, 2941, 2933, 2876, 2863, 2838, 1737, 1695, 1677, 1481, 1466, 1452, 1432, 1394, 1389, 1370, 1364, 1353, 1345, 1332, 1316, 1302, 1287, 1272, 1255, 1247, 1207, 1167, 1117, 1092, 1074, 1048, 1022, 1013, 966, 943, 934, 916, 879, 856, 841, 823, 808, 786, 758, 743, 690, 653, 605, 580, 534, 516, 499, 480, 449, 441, 416 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.27 (d, *J* = 1.7 Hz, 1H), 4.58 (bs, 1H), 4.55 – 4.46 (m, 1H), 2.49 (d, *J* = 12.1 Hz, 2H), 2.10 – 1.96 (m, 1H), 1.83 – 1.73 (m, 2H), 1.44 (s, 9H), 1.40 (s, 9H), 1.35 – 1.11 (m, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 171.0, 145.7, 115.1, 81.4, 70.6, 66.6, 61.4, 36.1, 28.5, 27.9, 25.8, 25.0, 23.6; **HRMS** (ESI) *m/z* 344.1899 [calcd for $C_{17}H_{30}NO_4S$ (M+H) 344.1896]; 366.1708 [calcd for $C_{17}H_{29}NO_4SNa$ (M+Na) 366.1715].



3.24k **3.25k**

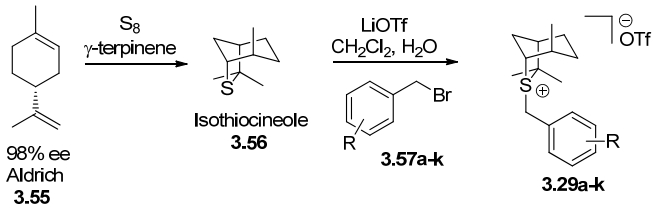
(+)-Dehydroproline **3.25k:** Aziridine **3.24k** (43.6 mg, 0.132 mmol, 1 equiv) was taken in a 5 mM solution of $Cu(hfacac)_2 \cdot H_2O$ in toluene (1.32 mL, 6.6 X 10^{-3} mmol, 0.05 equiv). The mixture was stirred in a sealed tube at 150 ºC for 5 h and then it was allowed to cool to room temperature and concentrated in vacuo The resultant brown solid was chromatographed on silica gel employing 9:1 hexanes:EtOAc as eluent to furnish **3.25k** (25.7 mg, 59% yield) as a colorless oil. Spectroscopic data for this material was identical to that for its enantiomer **3.25l** but with opposite optical rotation: **$[\alpha]_D^{21}$** -156.28° (*c* 0.15, $CHCl_3$); **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.45 (s, 1H), 5.14 (s, 1H), 4.97 (s, 1H), 2.36 – 2.12 (m, 2H), 2.12 – 1.83 (m, 4H), 1.46 (s, 9H), 1.41 (s, 9H).



3.24l **3.25l**

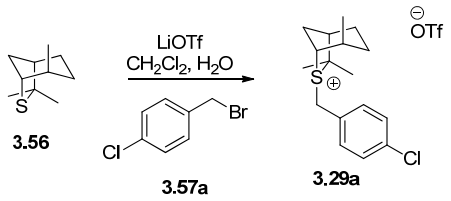
(-)-Dehydroproline **3.25l:** Azyridine **3.24l** (59.6 mg, 0.181 mmol, 1 equiv) was taken in a 5 mM solution of $Cu(hfacac)_2 \cdot H_2O$ in toluene (1.81 mL, 9.05 X 10^{-3} mmol, 0.05 equiv). The mixture was stirred in a sealed tube at 150 ºC for 5 h and then it was allowed to cool to room temperature and concentrated in vacuo The resultant brown solid was chromatographed on silica gel employing 9:1 hexanes:EtOAc as eluent to furnish **3.25l** (29.6 mg, 50% yield) as a brown oil.

$[\alpha]_D^{21}$ -124.62° (*c* 0.69, $CHCl_3$); **FTIR** (thin film/KCl) 2977, 2936, 2874, 1744, 1481, 1457, 1394, 1368, 1346, 1322, 1314, 1285, 1245, 1209, 1155, 1140, 1128, 1089, 1050, 1034, 1023, 1001, 981, 954, 913, 885, 850, 833, 808, 785, 742, 696, 670, 616, 581, 516 cm^{-1}; **^{1}H NMR** (300 MHz, $CDCl_3$) δ 5.45 (s, 1H), 5.14 (s, 1H), 4.97 (s, 1H), 2.36 – 2.12 (m, 2H), 2.12 – 1.83 (m, 4H), 1.46 (s, 9H), 1.41 (s, 9H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 170.8, 150.4, 113.4, 81.9, 75.7, 73.5, 61.2, 31.8, 28.1, 24.7, 24.1, 21.3; **HRMS** (ESI) *m/z* 330.1727 [calcd for $C_{16}H_{28}NO_4S$ (M+H) 330.1739].



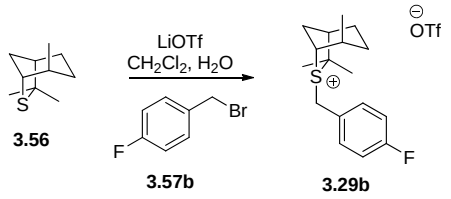
98% ee Aldrich **3.55** Isothiocineole **3.56** **3.57a-k** **3.29a-k**

General Procedure A: Isothiocineole[12] (1 equiv.) was dissolved in dichloromethane (1 mL for each 2.4 mmol of sulfide) and then the appropriate bromide (1.5 equiv) was added. Next, water (1 mL for each 5 mmol of LiOTf). and lithium triflate (5 eq.) were added. The biphasic mixture was stirred for 16 hours at room temperature. The reaction was diluted with more water and then extracted with CH_2Cl_2. The organic layer was dried with $NaSO_4$ and then concentrated. The crude product was dissolved in a minimum amount of dichloromethane and added dropwise to rapidly stirred diethyl ether. The precipitate was filtered and washed with diethyl ether.



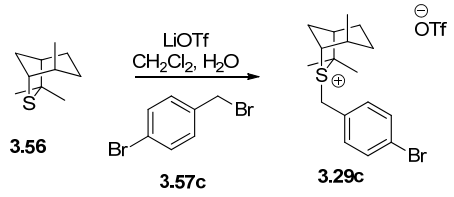
(1R,4R,5R,6R)-6-(4-Chlorobenzyl)-4,7,7-trimethyl-6-thiabicyclo[3.2.1]octane trifluoromethanesulfonate (**3.29a**): Synthesized according to general procedure A. Isothiocineole (0.500g) and 1-(bromomethyl)-4-chlorobenzene (1.246 g) yield sulfide **3.29a** (0.786 g, 60%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48 (d, *J* = 8.4, 2H), 7.21 (d, *J* = 8.4, 2H), 4.84 (d, *J* = 12.5, 1H), 4.46 (d, *J* = 12.6, 1H), 3.68 (s, 1H), 2.67 (d, *J* = 14.1, 1H), 2.34 – 2.21 (m, 2H), 1.98 (d, *J* = 3.2, 1H), 1.73 (s, 3H), 1.68 (s, 3H), 1.66 – 1.37 (m, 4H), 1.01 (d, *J* = 7.1, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 136.0, 132.2, 129.9, 127.8, 120.9 (q, *J* = 320.3), 72.9, 63.8, 50.5, 41.2, 32.2, 31.7, 25.4, 25.3, 23.1, 22.3, 17.9. **IR** (neat) 2940, 1493, 1467, 1259, 1156, 1030, 732, 637, 517 cm^{-1}. **HRMS** (ESI) m/z 295.1283 [calculated mass for $C_{17}H_{24}ClS$ (M^+-OTf) 295.1287].



(1R,4R,5R,6R)-6-(4-Fluorobenzyl)-4,7,7-trimethyl-6-thiabicyclo[3.2.1]octane trifluoromethanesulfonate (**19b**): Synthesized according to general procedure A. Isothiocineole (0.500g) and 1-(bromomethyl)-4-fluorobenzene (1.111 g) yield sulfide **3.29b** (0.925 g, 74%).

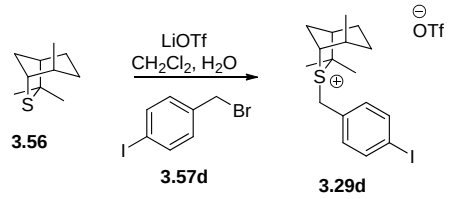
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (dd, *J* = 8.6, 5.2, 2H), 6.99 (t, *J* = 8.6, 2H), 4.90 (d, *J* = 12.5, 1H), 4.52 (d, *J* = 12.6, 1H), 3.75 (s, 1H), 2.73 (d, *J* = 14.2, 1H), 2.39 – 2.28 (m, 2H), 2.03 (d, *J* = 3.3, 1H), 1.78 (s, 3H), 1.73 (s, 3H), 1.70 – 1.41 (m, 4H), 1.06 (d, *J* = 7.1, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 163.5 (d, *J* = 250.4), 132.9 (d, *J* = 8.5), 125.1, 116.8 (d, *J* = 21.8), 72.8, 63.9, 50.6, 41.4, 32.2, 31.8, 25.5, 25.3, 23.2, 22.3, 17.9. **^{19}F NMR** (376.135 MHz, $CDCl_3$, C_6F_6) δ -81.31, -113.84. **IR** (neat) 2945, 1601, 1511, 1463, 1263, 1160, 1030, 856, 638, 517 cm^{-1}. **HRMS** (ESI) m/z 279.1573 [calculated mass for $C_{17}H_{24}F_3S$ (M^+-OTf) 279.1583].



3.56 3.57c 3.29c

(1R,4R,5R,6R)-6-(4-Bromobenzyl)-4,7,7-trimethyl-6-thiabicyclo[3.2.1]octane trifluoromethanesulfonate (**3.29c**): Synthesized according to general procedure A. Isothiocineole (0.500g) and 1-bromo-4-(bromomethyl)benzene (1.471 g) yield sulfide **3.29c** (0.918 g, 64%).

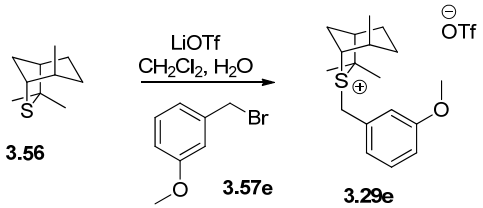
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (q, *J* = 8.6, 4H), 4.87 (d, *J* = 12.5, 1H), 4.51 (d, *J* = 12.6, 1H), 3.72 (s, 1H), 2.72 (d, *J* = 14.2, 1H), 2.37 – 2.27 (m, 2H), 2.03 (s, 1H), 1.78 (s, 3H), 1.73 (s, 3H), 1.70 – 1.43 (m, 4H), 1.06 (d, *J* = 7.1, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 132.9, 132.4, 128.3, 124.4, 120.9 (q, *J* = 320.1), 73.02, 63.9, 50.5, 41.3, 32.2, 31.8, 25.4, 25.3, 23.2, 22.3, 17.9. **IR** (neat) 2936, 1488, 1467, 1259, 1156, 1030, 729, 637, 517 cm^{-1}. **HRMS** (ESI) m/z 339.0779 [calculated mass for $C_{17}H_{24}BrS$ (M^+-OTf) 339.0782].



3.56 3.57d 3.29d

(1R,4R,5R,6R)-6-(4-Iodobenzyl)-4,7,7-trimethyl-6-thiabicyclo[3.2.1]octane trifluoromethanesulfonate (**3.29d**): Synthesized according to general procedure A. Isothiocineole (0.500g) and 1-(bromomethyl)-4-iodobenzene (1.379 g) yield sulfide **3.29d** (0.860 g, 55%).

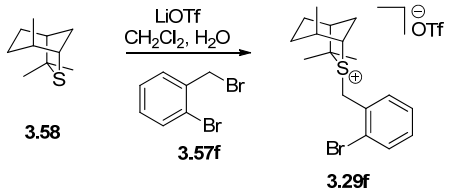
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, *J* = 8.4, 2H), 7.29 (d, *J* = 8.4, 2H), 4.87 (d, *J* = 12.5, 1H), 4.51 (d, *J* = 12.6, 1H), 3.73 (s, 1H), 2.73 (d, *J* = 13.7, 1H), 2.33 (t, *J* = 9.7, 2H), 2.06 (d, *J* = 3.4, 1H), 1.78 (s, 3H), 1.74 (s, 3H), 1.71 – 1.45 (m, 4H), 1.08 (d, *J* = 7.1, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.9, 132.5, 128.9, 96.5, 73.0, 64.0, 50.6, 41.5, 32.2, 31.8, 25.5, 25.3, 23.3, 22.4, 18.0. **IR** (neat) 2916, 1257, 1155, 1028, 637 cm^{-1}. **HRMS** (ESI) m/z 387.0649 [calculated mass for $C_{17}H_{24}IS$ (M^+-OTf) 387.0643].



3.56 3.57e 3.29e

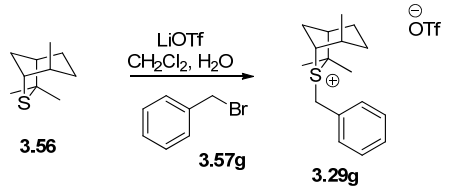
(1*R*,4*R*,5*R*,6*R*)-6-(3-Methoxybenzyl)-4,7,7-trimethyl-6-thiabicyclo[3.2.1]octane trifluoromethanesulfonate (**3.29e**): Synthesized according to general procedure A. Isothiocineole (0.500g) and 1-(bromomethyl)-3-methoxybenzene (1.183 g) yield sulfide **3.29e** (0.937 g, 72%)..

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25 – 7.16 (m, 2H), 7.07 (d, *J* = 7.7, 1H), 6.87 – 6.78 (m, 1H), 4.89 (d, *J* = 12.5, 1H), 4.47 (d, *J* = 12.5, 1H), 3.80 (s, 4H), 2.76 – 2.68 (m, 1H), 2.34 (t, *J* = 10.1, 2H), 2.06 (s, 1H), 1.80 (s, 3H), 1.75 (s, 3H), 1.73 – 1.42 (m, 4H), 1.07 (d, *J* = 7.1, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.5, 130.7, 130.5, 122.7, 116.7, 114.9, 72.6, 63.9, 55.7, 50.6, 42.3, 32.2, 31.8, 25.5, 25.4, 23.3, 22.4, 18.0. **IR** (neat) 2931, 1600, 1467, 1260, 1154, 1030, 647 cm^{-1}. **HRMS** (ESI) m/z 291.1776 [calculated mass for $C_{18}H_{27}OS$ (M^+-OTf) 291.1783].



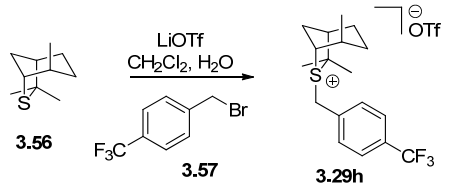
(1S,4S,5S,6S)-6-(4-Bromobenzyl)-4,7,7-trimethyl-6-thiabicyclo[3.2.1]octane trifluoromethanesulfonate (**3.29f**): Synthesized according to general procedure A. Isothiocineole (0.485 g) and 1-bromo-2-(bromomethyl)benzene (1.07 g) yield sulfide **3.29f** (0.863 g, 62%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 6.7, 1H), 7.64 (d, *J* = 7.9, 1H), 7.45 (t, *J* = 7.2, 1H), 7.33 (td, *J* = 7.9, 1.3, 1H), 4.99 (d, *J* = 13.0, 1H), 4.70 (d, *J* = 13.0, 1H), 4.18 (s, 1H), 2.92 (d, *J* = 14.9, 1H), 2.50 (s, 1H), 2.12 (d, *J* = 3.8, 1H), 1.89 (s, 3H), 1.88 (s, 3H), 1.85 – 1.53 (m, 5H), 1.17 (d, *J* = 7.1, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 133.9, 133.6, 132.2, 129.7, 128.7, 125.3, 73.3, 65.1, 50.4, 42.9, 32.8, 32.6, 26.6, 25.3, 23.6, 22.4, 18.0. **IR** (neat) 2936, 1469, 1258, 1224, 1154, 1029, 637 cm^{-1}.



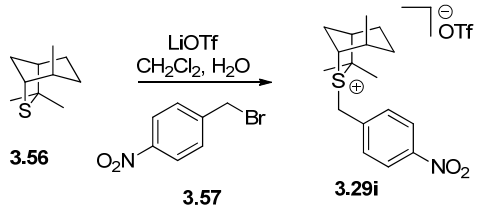
(1R,4R,5R,6R)-6-Benzyl-4,7,7-trimethyl-6-thiabicyclo[3.2.1]octane trifluoromethanesulfonate (**3.29g**): Synthesized according to general procedure A. Isothiocineole (1.000 g) and benzyl bromide (2.012 g) yield sulfide **19g** (01.875 g, 78%). Compound matches existing literature data.[13]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, *J* = 7.2, 2.2, 2H), 7.44 – 7.38 (m, 2H), 4.89 (d, *J* = 12.6, 1H), 4.58 (d, *J* = 12.9, 1H), 3.95 (s, 1H), 2.72 (s, 1H), 2.43 (d, *J* = 13.5, 2H), 2.16 (s, 1H), 1.83 (s, 3H), 1.80 (s, 3H), 1.77 – 1.58 (m, 4H), 1.13 (d, *J* = 7.1, 3H).



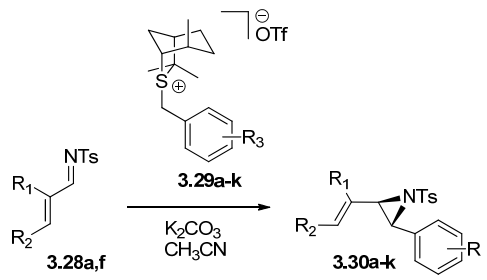
(1R,4R,5R,6R)-6-(4-(Trifluoromethyl)benzyl)-4,7,7-trimethyl-6-thiabicyclo[3.2.1]octane trifluoromethanesulfonate (**19h**): Synthesized according to general procedure A. Isothiocineole (0.500 g) and 1-(bromomethyl)-4-(trifluoromethyl)benzene (1.07 g) yield sulfide **19h** (0.869 g, 62%).

^{1}H NMR (400 MHz, CDC_3) δ 7.72 (d, *J* = 8.1, 2H), 7.60 (d, *J* = 7.9, 2H), 5.00 (d, *J* = 12.9, 1H), 4.71 (d, *J* = 12.8, 1H), 3.86 (s, 1H), 2.77 (d, *J* = 14.1, 1H), 2.40 (d, *J* = 13.7, 2H), 2.14 (s, 1H), 1.82 (s, 3H), 1.78 (s, 3H), 1.75 – 1.48 (m, 4H), 1.12 (d, *J* = 7.1, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 133.7, 131.9 (q, *J* = 32.8), 131.2, 126.6 (q, *J* = 3.6), 123,7 (q, *J* = 272.5), 120.9 (q, *J* = 320.1), 73.4, 64.4, 50.6, 41.2, 32.2, 31.9, 25.5, 25.3, 23.3, 22.3, 17.9. **IR** (neat) 2946, 1462, 1420, 1352, 1253, 1159, 1134, 1111, 1067, 1028, 855, 638 cm^{-1}. **^{19}F NMR** (376.135 MHz, $CDCl_3$, C_6F_6) δ -81.47, -66.21. **HRMS** (ESI) m/z 329.1546 [calculated mass for $C_{18}H_{24}F_3S$ (M^+-OTf) 329.1551].

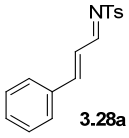


(1R,4R,5R,6R)-6-(4-Nitrobenzyl)-4,7,7-trimethyl-6-thiabicyclo[3.2.1]octane trifluoromethanesulfonate (**19i**): Synthesized according to general procedure A. Isothiocineole (0.500 g) and 1-(bromomethyl)-4-nitrobenzene (0.953 g) yield sulfide **3.29i** (0.852 g, 64%).

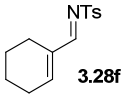
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.7, 2H), 7.82 (d, *J* = 8.8, 2H), 5.07 (d, *J* = 13.0, 1H), 4.78 (d, *J* = 13.0, 1H), 3.85 (s, 1H), 2.77 (d, *J* = 14.6, 1H), 2.45 – 2.34 (m, 2H), 2.14 (s, 1H), 1.83 (s, 3H), 1.78 (s, 3H), 1.76 – 1.50 (m, 4H), 1.11 (d, *J* = 7.1, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.6, 136.9, 132.0, 124.7, 120.8 (q, *J* = 320.2), 74.0, 64.7, 50.6, 40.8, 32.2, 32.0, 25.6, 25.3, 23.3, 22.3, 17.9. **IR** (neat) 2994, 2944, 1605, 1527, 1464, 1350, 1254, 1226, 1162, 1028, 860, 717, 639 cm^{-1}. **HRMS** (ESI) m/z 306.1517 [calculated mass for $C_{17}H_{24}NO_2S$ (M^+-OTf) 306.1528].



General Procedure B: In a typical experimental procedure sulfonium salt (~0.1 mmol, 1 eq.) was dissolved in acetonitrile (0.1 M). Then the imine (1.0 eq.) was added and placed in a 0 °C bath. Next, K_2CO_3 (2.0 eq.) was added and the solution was stirred for 12-36 hours at room temperature. The reaction was quenched by addition of water and then extracted with CH_2Cl_3. The organic layer was dried with Na_2SO_4 and then concentrated. The product was purified by silica gel chromatography.

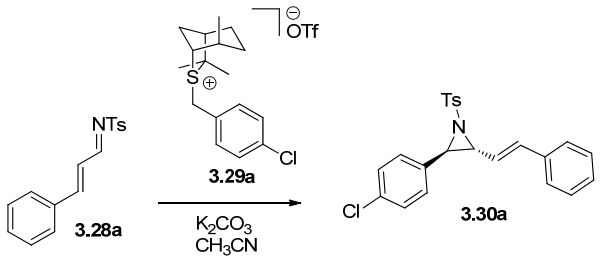


N-Benzylidene-4-methylbenzenesulfonamide (**3.28a**): Prepared according to known method[14] and has been previously characterized.[15]



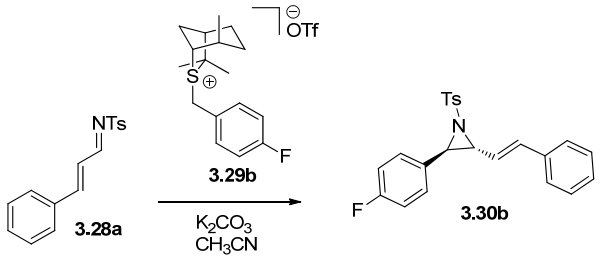
N-Cyclohexenylmethylen-4-methylbenzenesulfonamide (**3.28f**): A mixture of 1-Cyclohexene-1-carboxaldehyde (0.10g, 0.91 mmol, 1 equiv.), p-Toluenesulfonamide (0.155g, 0.91 mmol, 1 equiv.), activated MS 4A and catalytic amount of Amberlyst-15 in dry toluene (5 mL) was heated in a sealed tube for 12 h. The mixture was filtered through Celite and concentrated. The resulting yellow oil was used in the next reaction (mostly pure) or can be purified by silica gel flash chromatography (slightly unstable). Yield 215 mg (90%).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 8.40 (s, 1H), 7.72 (d, *J* = 8.2 Hz, 2H), 7.22 (d, *J* = 8.2 Hz, 2H), 6.75-6.71 (m, 1H), 2.33 (s, 3H), 2.29-2.20 (m, 2H), 2.19-2.13 (m, 2H), 1.59-1.50 (m, 4H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 172.3, 153.8, 144.1, 137.2, 135.6, 129.6, 127.8, 27.3, 22.7, 21.6, 21.5, 21.2. **IR** (neat) 2934, 2863, 1628, 1567, 1319, 1158, 1090, 930, 807, 777, 696, 655, 568 cm^{-1}. **ESMS** m/z 264.1 ($[M+H]^+$); **HRMS** (ESI) m/z calcd for $C_{14}H_{18}NO_2S$ ($[M+H]^+$) 264.1058 found 264.1058.



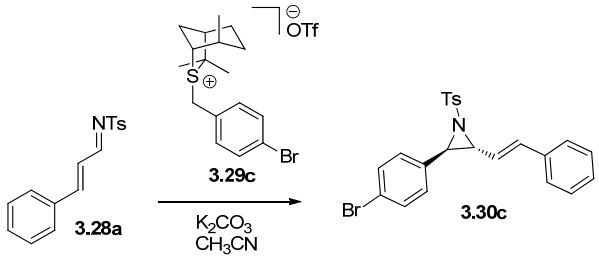
(2R,3R)-2-(4-Chlorophenyl)-3-((E)-styryl)-1-tosylaziridine 3.30): Synthesized according to general procedure B. 4-methyl-N-((E)-3-phenylallylidene)benzenesulfonamide (0.100 g) and sulfide salt **3.29a** (0.156 g) yield aziridine **3.30a** (0.055 g, 38%, d.r.= >20:1).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3, 2H), 7.36 (d, *J* = 7.1, 2H), 7.28 (dd, *J* = 8.1, 6.7, 2H), 7.24 – 7.18 (m, 5H), 7.08 (d, *J* = 8.5, 2H), 6.73 (d, *J* = 15.8, 1H), 6.56 (dd, *J* = 15.8, 9.6, 1H), 4.04 (d, *J* = 4.0, 1H), 3.33 (dd, *J* = 9.6, 4.0, 1H), 2.33 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 144.6, 137.9, 136.9, 136.0, 134.4, 133.8, 129.9, 129.1, 128.9, 128.7, 127.9, 127.8, 127.0, 122.0, 55.5, 48.2, 21.9. **IR** (neat) 1597, 1493, 1326, 1159, 1088, 900, 694 cm^{-1}. **HRMS** (ESI) m/z 410.0971 [calculated mass for $C_{23}H_{21}ClNO_2S$ ($M+H^+$) 410.0982].



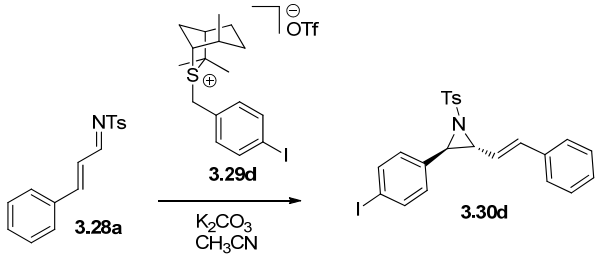
(*2R,3R)-2-(4-Fluorophenyl)-3-((E)-styryl)-1-tosylaziridine* (**3.30b**): Synthesized according to general procedure B. 4-methyl-N-((E)-3-phenylallylidene)benzenesulfonamide (0.100 g) and sulfide salt **3.29b** (0.150 g) yield aziridine **3.30b** (0.097 g, 70%, d.r.= >20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3, 2H), 7.35 (d, *J* = 7.2, 2H), 7.27 (t, *J* = 7.3, 2H), 7.24 – 7.15 (m, 2H), 7.14 – 7.08 (m, 3H), 6.90 (t, *J* = 8.6, 2H), 6.71 (d, *J* = 15.8, 1H), 6.56 (dd, *J* = 15.8, 9.6, 1H), 4.06 (d, *J* = 4.1, 1H), 3.33 (dd, *J* = 9.6, 4.1, 1H), 2.31 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.8 (d, *J* = 246.9), 144.6, 137.8, 136.9, 136.0, 131.0, 129.8, 128.9, 128.6, 128.2 (d, *J* = 8.3), 127.7, 126.9, 122.0, 115.8 (d, *J* = 21.8), 55.4, 48.2, 21.8. **^{19}F NMR** (376.135 MHz, $CDCl_3$, C_6F_6) δ -116.61. **IR** (neat) 3056, 1599, 1494, 1327, 1231, 1160, 901, 837, 694 cm^{-1}. **HRMS** (ESI) m/z 394.1270 [calculated mass for $C_{23}H_{21}FNO_2S$ ($M+H^+$) 394.1277].



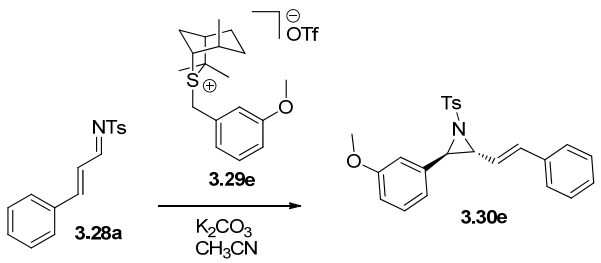
(2R,3R)-2-(4-Bromophenyl)-3-((E)-styryl)-1-tosylaziridinetosylaziridine (**3.30c**): Synthesized according to general procedure B. 4-methyl-N-((E)-3-phenylallylidene)benzenesulfonamide (0.100 g) and sulfide salt **3.29c** (0.188g) yield aziridine **3.30c** (0.057 g, 38%, d.r.= >20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.3, 2H), 7.35 (t, *J* = 7.7, 4H), 7.28 (dd, *J* = 8.1, 6.5, 2H), 7.25 – 7.17 (m, 3H), 7.02 (d, *J* = 8.5, 2H), 6.72 (d, *J* = 15.8, 1H), 6.56 (dd, *J* = 15.8, 9.6, 1H), 4.03 (d, *J* = 4.0, 1H), 3.33 (dd, *J* = 9.6, 4.1, 1H), 2.32 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.6, 137.9, 136.8, 136.0, 134.4, 132.0, 129.9, 128.9, 128.7, 128.1, 127.7, 127.0, 122.5, 121.9, 55.5, 48.2, 21.9. **IR** (neat) 3028, 1652, 1489, 1301, 1156, 1085, 968, 902, 817, 745, 649, 536 cm^{-1}**. HRMS** (ESI) m/z 454.0479 [calculated mass for $C_{23}H_{21}BrNO_2S$ ($M+H^+$) 454.0476].



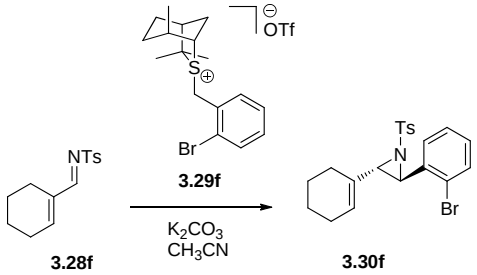
(2R,3R)-2-(4-Iodophenyl)-3-((E)-styryl)-1-tosylaziridine (**3.30d**): Synthesized according to general procedure B. 4-methyl-N-((E)-3-phenylallylidene)benzenesulfonamide (0.100 g) and sulfide salt **3.29d** (0.188g) yield aziridine **3.30d** (0.047 g, 28%, d.r.= >20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 8.3, 2H), 7.61 (d, *J* = 8.4, 2H), 7.43 (d, *J* = 7.0, 2H), 7.35 (t, *J* = 7.3, 2H), 7.31 – 7.23 (m, 3H), 7.02 – 6.90 (m, 2H), 6.80 (d, *J* = 15.8, 1H), 6.64 (dd, *J* = 15.8, 9.6, 1H), 4.09 (s, 1H), 3.40 (dd, *J* = 9.6, 4.0, 1H), 2.40 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.6, 137.9(1), 137.9(0), 136.8, 136.0, 135.0, 129.8, 128.9, 128.6, 128.3, 127.7, 126.9, 121.9, 94.0, 55.5, 48.3, 21.8. **IR** (neat) 1597, 1485, 1327, 1159, 1092, 1006, 911, 813, 748, 694 cm^{-1}. **HRMS** (ESI) m/z 502.0349 [calculated mass for $C_{23}H_{21}INO_2S$ ($M+H^+$) 502.0338].



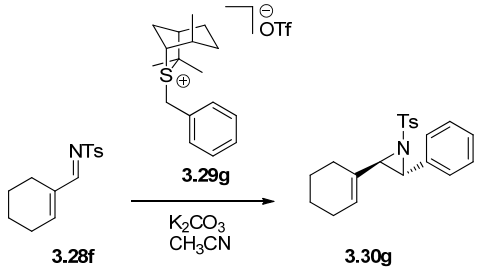
(2R,3R)-2-((E)-3-Methoxystyryl)-3-phenyl-1-tosylaziridine (**3.30e**): Synthesized according to general procedure B. 4-methyl-N-((E)-3-phenylallylidene)benzenesulfonamide (0.183 g) and sulfide salt **3.29e** (0.283 g) yield aziridine **3.30e** (0.093 g, 36%, d.r.= >20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, *J* = 8.3, 2H), 7.44 (d, *J* = 7.0, 2H), 7.35 (dd, *J* = 8.1, 6.6, 2H), 7.31 – 7.25 (m, 3H), 7.20 (t, *J* = 7.9, 1H), 6.85 – 6.77 (m, 3H), 6.72 – 6.70 (m, 1H), 6.66 (dd, *J* = 15.8, 9.6, 1H), 4.13 (d, *J* = 4.1, 1H), 3.74 (s, 3H), 3.44 (dd, *J* = 9.6, 4.1, 1H), 2.39 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 160.0, 144.5, 137.7, 137.1, 136.9, 136.1, 129.9, 129.8, 128.9, 128.6, 127.8, 127.0, 122.3, 118.9, 114.2, 111.6, 55.5, 55.4, 48.9, 21.8. **IR** (neat) 3059, 2961, 1599, 1493, 1325, 1060, 1088, 1044, 902, 695 cm^{-1}. **HRMS** (ESI) m/z 406.1482 [calculated mass for $C_{24}H_{24}NO_3S$ ($M+H^+$) 406.1477].



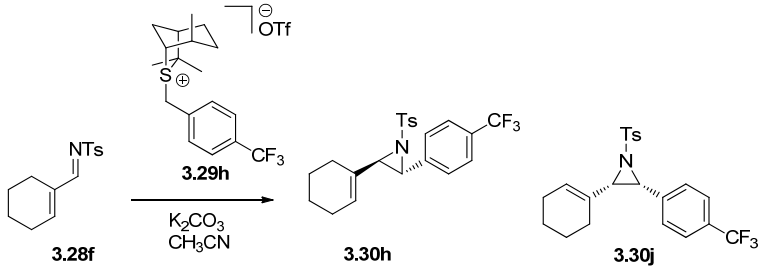
(2S,3S)-2-(2-Bromophenyl)-3-(cyclohex-1-en-1-yl)-1-tosylaziridine (**3.30f**): Synthesized according to general procedure B. N-(cyclohex-1-en-1-ylmethylene)-4-methylbenzenesulfonamide (0.155 g) and sulfide salt **3.29f** (0.289 g) yield aziridine **3.30f** (0.163 g, 64%, d.r.= ~10:1 trans:cis).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, *J* = 8.3, 2H), 7.51 (dd, *J* = 7.7, 1.1, 1H), 7.27 (d, *J* = 9.1, 2H), 7.21 – 7.09 (m, 3H), 6.09 (s, 1H), 4.37 (d, *J* = 4.9, 1H), 3.36 (d, *J* = 4.7, 1H), 2.42 (s, 3H), 2.32 – 2.17 (m, 2H), 2.10 (d, *J* = 2.5, 2H), 1.76 – 1.58 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.1, 137.5, 134.7, 132.6, 130.9, 129.8, 129.6, 129.5, 128.5, 127.8, 127.6, 124.2, 55.8, 47.0, 27.2, 25.7, 22.7, 22.1, 21.8. **IR** (neat) 2929, 1596, 1438, 1329, 1161, 1086, 1025, 937, 906, 814, 752, 708, 692, 541 cm^{-1}.

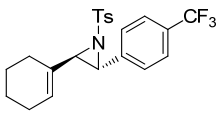


(2R,3R)-2-(Cyclohex-1-en-1-yl)-3-phenyl-1-tosylaziridine (**3.30g**): Synthesized according to general procedure B. N-(cyclohex-1-en-1-ylmethylene)-4-methylbenzenesulfonamide (0.250 g) and sulfide salt **3.29g** (0.195 g) yield aziridine **3.30g** (0.163 g, 79%, d.r.= ~6:1 trans:cis).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, *J* = 8.3, 2H), 7.30 – 7.25 (m, 5H), 7.23 (d, *J* = 8.0, 2H), 5.95 (d, *J* = 1.1, 1H), 4.08 (d, *J* = 4.9, 1H), 3.62 (d, *J* = 4.3, 1H), 2.39 (s, 3H), 2.17 – 2.03 (m, 4H), 1.77 – 1.54 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.9, 137.7, 133.8, 130.5, 129.5(4), 129.5(3), 128.6, 128.5 128.2, 127.6, 53.9, 48.0, 26.6, 25.5, 22.6, 22.2, 21.8. **IR** (neat) 2928, 1597, 1453, 1325, 1160, 1086, 935, 902, 813, 691, 636 cm^{-1}. **HRMS** (ESI) m/z 354.1528 [calculated mass for $C_{21}H_{24}NO_2S$ (M^+) 354.1528].



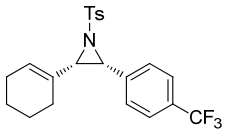
Synthesized according to general procedure B. N-(cyclohex-1-en-1-ylmethylene)-4-methylbenzenesulfonamide (0.300 g) and sulfide salt **3.29h** (0.545 g) yield aziridine **3.30h** and **3.30j** (0.392 g, 82%, d.r.= ~6:1 trans(**3.30h**):cis(**3.30j**)).



(2R,3R)-2-(Cyclohex-1-en-1-yl)-1-tosyl-3-(4-(trifluoromethyl)phenyl)aziridine (**3.30h**):

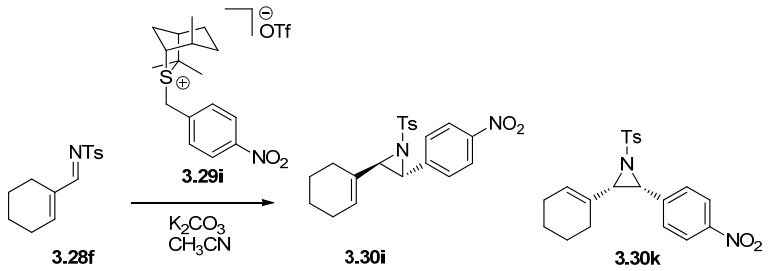
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, *J* = 8.3, 2H), 7.54 (d, *J* = 8.1, 2H), 7.39 (d, *J* = 8.5, 2H), 7.25 (dd, *J* = 8.5, 0.6, 2H), 6.00 – 5.94 (m, 1H), 4.12 (d, *J* = 4.7, 1H), 3.56 (d, *J* = 4.0, 1H), 2.41 (s, 3H), 2.16 – 2.06 (m, 4H), 1.74 – 1.55 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 144.2, 138.2, 137.4, 130.5 (q, *J* = 32.5), 130.0(2), 129.9(6)

129.6, 128.4, 127.5, 125.4 (q, J = 3.8), 121.4 (q, J = 272.1), 54.6, 46.7, 26.6, 25.5, 22.5, 22.0, 21.7. **IR** (neat) 2930, 1920, 1804, 1620, 1598, 1434, 1404, 1323, 1162, 912, 813, 693, 535 cm^{-1}. **^{19}F NMR** (376.135 MHz, $CDCl_3$, C_6F_6) δ -65.78. **HRMS** (ESI) m/z 422.1401 [calculated mass for $C_{22}H_{23}F_3NO_2S$ ($M+H^+$) 422.1402].

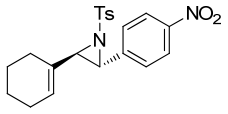


(2S,3R)-2-(Cyclohex-1-en-1-yl)-1-tosyl-3-(4-(trifluoromethyl)phenyl)aziridine (**3.30j**):

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.89 (d, J = 8.3, 2H), 7.48 (d, J = 8.1, 2H), 7.35 (dd, J = 8.5, 0.6, 2H), 7.28 (d, J = 8.6, 2H), 5.72 – 5.56 (m, 1H), 3.99 (d, J = 7.3, 1H), 3.57 (dd, J = 7.3, 1.3, 1H), 2.45 (s, 3H), 1.91 – 1.75 (m, 2H), 1.72 – 1.61 (m, 1H), 1.44 – 1.31 (m, 3H), 1.28 – 1.18 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.0, 137.2, 135.0, 130.1 (q, J = 32.4), 130.0, 128.2, 128.1, 127.9(2), 127.8(9), 124.9 (q, J = 3.8), 124.3 (q, J = 272.1), 49.5, 45.7, 26.4, 24.8, 22.2, 22.1, 21.9. **IR** (neat) 2928, 1621, 1324, 1161, 1124, 1066, 1017, 900, 846, 677, 564 cm^{-1}. **^{19}F NMR** (376.135 MHz, $CDCl_3$, C_6F_6) δ -65.70. **HRMS** (ESI) m/z 422.1396 [calculated mass for $C_{22}H_{23}F_3NO_2S$ ($M+H^+$) 422.1402].



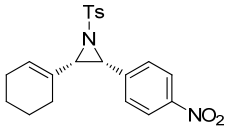
Synthesized according to general procedure B. N-(cyclohex-1-en-1-ylmethylene)-4-methylbenzenesulfonamide (0.300 g) and sulfide salt **3.29i** (0.519 g) yield aziridine **3.30i** and **3.30k** (0.334 g, 74%, d.r.= ~6:1 trans(**3.30i**):cis(**3.30k**)).



(2R,3R)-2-(Cyclohex-1-en-1-yl)-3-(4-nitrophenyl)-1-tosylaziridine (**3.30i**)

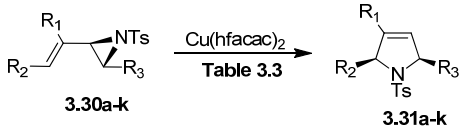
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8.8, 2H), 7.74 (d, J = 8.3, 2H), 7.45 (d, J = 8.7, 2H), 7.28 (d, J = 8.2, 2H), 5.98 (d, J = 1.0, 1H), 4.16 (d, J = 4.7, 1H), 3.56 (d, J = 4.0, 1H), 2.42 (s, 3H), 2.17 – 2.05 (m, 4H), 1.71 – 1.57 (m, 4H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.0, 144.5, 141.8, 137.4, 130.5, 129.8, 129.7, 128.9, 127.6, 123.8, 55.3,

46.3, 26.7, 25.6, 22.5, 22.0, 21.8. **IR** (neat) 2930, 1659, 1599, 1519, 1345, 1159, 667 cm^{-1}. **HRMS** (ESI) m/z 399.1381 [calculated mass for $C_{21}H_{23}N_2O_4S$ ($M+H^+$) 399.1379].

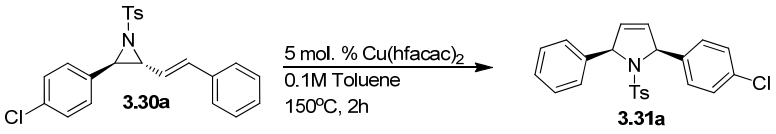


(2S,3R)-2-(Cyclohex-1-en-1-yl)-3-(4-nitrophenyl)-1-tosylaziridine (**20k**)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.6, 2H), 7.89 (d, *J* = 8.2, 2H), 7.36 (d, *J* = 6.1, 2H), 7.34 (d, *J* = 7.0, 2H), 5.63 (s, 1H), 4.02 (d, *J* = 7.3, 1H), 3.60 (d, *J* = 7.1, 1H), 2.46 (s, 3H), 1.91 – 1.77 (m, 2H), 1.74 – 1.62 (m, 1H), 1.45 – 1.16 (m, 5H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 147.7, 145.2, 140.6, 134.8, 130.1, 128.6, 128.21(9), 128.1(6), 127.6, 123.2, 49.8, 45.3, 26.4, 24.8, 22.1(3), 22.0(7), 21.9. **IR** (neat) 2927, 1600, 1520, 1345, 1161, 1091, 895, 854, 678, 565 cm^{-1}.



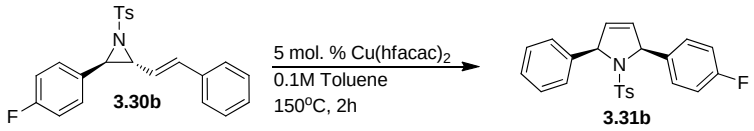
General Procedure C: To a flame dried 13x100 mm threaded culture tube was added $Cu(hfacac)_2$ (1.3 mg, 0.00246 mmol, 0.05 equiv.) and then evacuated and filled with nitrogen. Then a solution of the vinylazirdine **3.30** (0.025 g, 0.045 mmol) in dry toluene (0.5 mL) is added. The vial was fitted with a teflon cap and submerged in an oil bath at 150ºC until reaction was complete by TLC. The reaction was concentrated and purified by silica gel chromatography to yield **3.31** (71-97% yield, diastereomeric ratio >20:1).



(2S,5R)-2-(4-Chlorophenyl)-5-phenyl-1-tosyl-2,5-dihydro-1H-pyrrole (**3.31a**): Synthesized according to general procedure C to yield pyrroline **3.31a** (84%, d.r.= >20:1).

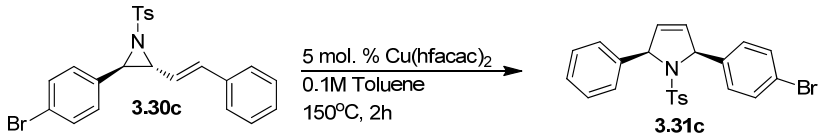
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.17 (m, 13H), 5.72 (d, *J* = 6.0, 1H), 5.67 (d, *J* = 6.0, 1H), 5.63 (d, *J* = 2.1, 1H), 5.60 (d, *J* = 2.0, 1H), 2.28 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.6, 140.1, 138.9, 135.9, 133.9, 130.0 129.5, 129.3, 129.0, 128.8, 128.7, 128.1, 127.9, 127.7, 71.0 70.3, 21.7. **IR** (neat) 3063, 2927, 1597, 1491, 1349,

1163, 1090, 1046, 817, 664, 598, 547 cm^{-1}. **HRMS** (ESI) m/z 410.0990 [calculated mass for $C_{23}H_{21}ClNO_2S$ ($M+H^+$) 410.0982].



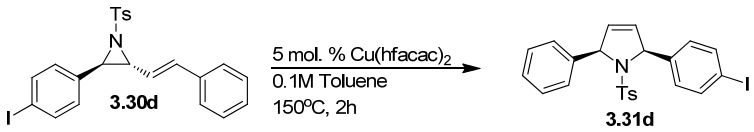
(2S,5R)-2-(4-Fluorophenyl)-5-phenyl-1-tosyl-2,5-dihydro-1H-pyrrole (**3.31b**): Synthesized according to general procedure C to yield pyrroline **3.31b** (91%, d.r.= >20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.27 (m, 13H), 5.80 (d, *J* = 6.0, 1H), 5.75 (d, *J* = 6.0, 1H), 5.71 (s, 2H), 2.35 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 162.6 (d, *J* = 246.3), 143.5, 140.2, 136.2, 136.0, 129.8, 129.7 (d, *J* = 8.3), 129.5, 129.2, 128.7, 128.1, 127.9, 127.6, 115.4 (d, *J* = 21.6), 70.9, 70.2, 21.7. **^{19}F NMR** (376.135 MHz, $CDCl_3$, C_6F_6) δ-117.80. **IR** (neat) 3065, 2924, 1676, 1601, 1508, 1349, 1224, 1163, 1091, 1046, 828, 665, 599 cm^{-1}. **HRMS** (ESI) m/z 394.1269 [calculated mass for $C_{23}H_{21}FNO_2S$ ($M+H^+$) 394.1277].



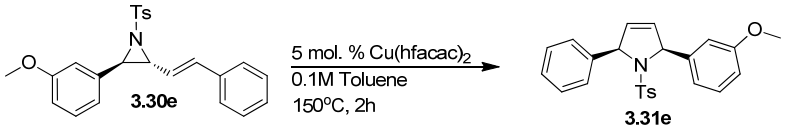
(2S,5R)-2-(4-Bromophenyl)-5-phenyl-1-tosyl-2,5-dihydro-1H-pyrrole (**3.31c**): Synthesized according to general procedure C to yield pyrroline **3.31c** (92%, d.r.= >20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.5, 2H), 7.35 (d, *J* = 8.3, 2H), 7.34 – 7.25 (m, 5H), 7.22 (d, *J* = 8.4, 2H), 7.10 (d, *J* = 8.0, 2H), 5.79 (dt, *J* = 6.0, 2.0, 1H), 5.74 (dt, *J* = 6.0, 2.1, 1H), 5.70 (dd, *J* = 4.6, 2.2, 1H), 5.66 (dd, *J* = 4.3, 2.1, 1H), 2.36 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.6, 140.1, 139.5, 135.9, 131.7, 130.0, 129.7, 129.5, 129.0, 128.7, 128.2, 127.9, 127.7, 122.0, 71.0, 70.3, 21.7. **IR** (neat) 1596, 1484, 1348, 1162, 1093, 1010, 816, 662, 596, 546 cm^{-1}. **HRMS** (ESI) m/z 454.0465 [calculated mass for $C_{23}H_{21}BrNO_2S$ ($M+H^+$) 454.0476].



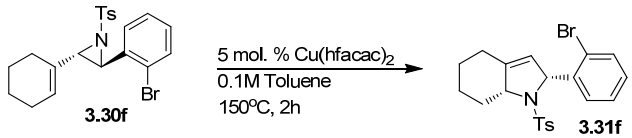
(2S,5R)-2-(4-Iodophenyl)-5-phenyl-1-tosyl-2,5-dihydro-1H-pyrrole (**3.31d**): Synthesized according to general procedure C to yield pyrroline **3.31d** (87%, d.r.= >20:1.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.2, 2H), 7.38 – 7.27 (m, 7H), 7.12 – 7.07 (m, 4H), 5.79 (dt, *J* = 5.8, 2.0, 1H), 5.76 – 5.72 (m, 1H), 5.70 (d, *J* = 2.2, 1H), 5.63 (d, *J* = 2.1, 1H), 2.36 (s, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 143.6, 140.1(3), 140.1(1), 137.7, 135.9, 130.0, 129.9, 129.5, 129.0, 128.7, 128.2, 127.9, 127.7, 93.7, 71.0, 70.4, 21.7. **IR** (neat) 2921, 1674, 1597, 1482, 1349, 1163, 1091, 1048, 1006, 815, 697, 667, 597, 546 cm^{-1}. **HRMS** (ESI) m/z 502.0335 [calculated mass for $C_{23}H_{21}INO_2S$ ($M+H^+$) 502.0338].



(2S,5R)-2-(3-Methoxyphenyl)-5-phenyl-1-tosyl-2,5-dihydro-1H-pyrrole (**3.31e**): Synthesized according to general procedure C to yield pyrroline **3.31e** (81%, d.r.= >20:1).

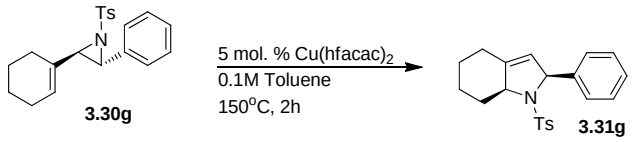
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (dd, *J* = 7.9, 1.6, 2H), 7.38 – 7.28 (m, 5H), 7.21 (td, *J* = 7.5, 1.2, 1H), 7.08 (d, *J* = 8.0, 2H), 6.94 (dd, *J* = 4.9, 3.8, 1H), 6.83 – 6.75 (m, 2H), 5.80 – 5.75 (m, 3H), 5.69 (d, *J* = 1.7, 1H), 3.65 (s, 3H), 2.34 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 159.8, 143.3, 141.8, 140.4, 136.2, 129.8, 129.6, 129.4, 129.1, 128.6, 128.2, 128.1, 127.7, 120.1, 114.2, 112.6, 71.0, 70.8, 55.2, 21.7. **IR** (neat) 2918, 1599, 1492, 1452, 1162, 1090, 1042, 761, 693, 665, 594, 545 cm^{-1}. **HRMS** (ESI) m/z 406.1467 [calculated mass for $C_{24}H_{24}NO_3S$ ($M+H^+$) 406.1477].



(2R,7aR)-2-(2-Bromophenyl)-1-tosyl-2,4,5,6,7,7a-hexahydro-1H-indole (**3.31f**): Synthesized according to general procedure C to yield pyrroline **3.31f** (97%, d.r.= >20:1).

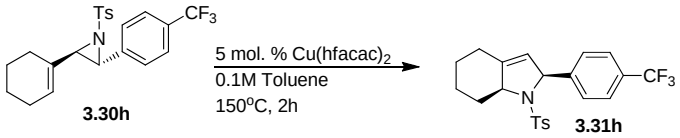
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, *J* = 8.2, 2H), 7.62 (dd, *J* = 7.8, 1.7, 1H), 7.49 (dd, *J* = 8.0, 1.1, 1H), 7.35 – 7.28 (m, 3H), 7.10 (td, *J* = 7.7, 1.7, 1H), 5.75 (bs, 1H), 5.22 (d, *J* = 1.8, 1H), 4.14 (dd, *J* = 10.8, 5.3, 1H), 2.69 – 2.61 (m, 1H), 2.42 (s, 3H), 2.39 – 2.31 (m, 1H), 1.94 – 1.82 (m, 2H), 1.78 (d, *J* = 13.0, 1H), 1.66 – 1.56 (m, 1H), 1.50 – 1.37 (m, 1H), 1.34 – 1.12 (m, 1H). **^{13}C NM**R (101 MHz, $CDCl_3$) δ 143.8, 141.0, 140.8, 134.4, 132.6, 129.9, 129.2, 128.9, 128.1(4), 128.0(9), 122.0, 119.2, 70.1,

67.8, 37.6, 28.3, 26.5, 24.2, 21.8. **IR** (neat) 2931, 1683, 1506, 1348, 1164, 1094, 1062, 753, 659 cm^{-1}.



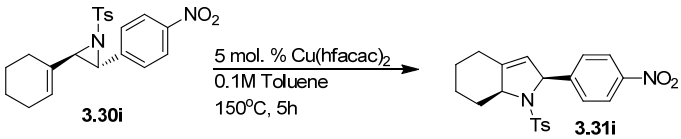
(2S,7aS)-2-Phenyl-1-tosyl-2,4,5,6,7,7a-hexahydro-1H-indole (**3.31g**): Synthesized according to general procedure C to yield pyrroline **3.31g** (92%, d.r.= >20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.2, 2H), 7.34 – 7.19 (m, 7H), 5.41 (d, *J* = 2.1, 1H), 5.12 (d, *J* = 1.6, 1H), 4.22 (dd, *J* = 9.5, 5.2, 1H), 2.53 – 2.46 (m, 1H), 2.45 – 2.42 (m, 1H), 2.39 (s, 3H), 1.94 (t, *J* = 13.4, 1H), 1.82 (dd, *J* = 16.7, 6.9, 2H), 1.58 – 1.36 (m, 2H), 1.33 – 1.18 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.3, 141.9, 140.9, 136.0, 129.7, 128.6, 127.7(3), 127.6(8), 127.4, 120.1, 70.6, 67.4, 37.3, 28.4, 26.8, 24.2, 21.7. **IR** (neat) 2932, 1455, 1348, 1163, 1096, 1038, 757, 660, 589, 566 cm^{-1}. **HRMS** (ESI) m/z 354.1523 [calculated mass for $C_{21}H_{24}NO_2S$ ($M+H^+$) 354.1522].



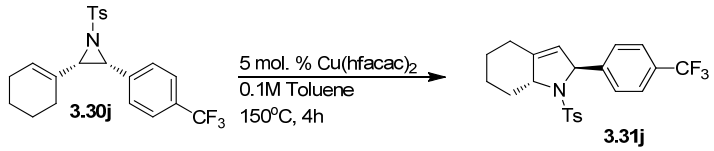
(2S,7aS)-1-Tosyl-2-(4-(trifluoromethyl)phenyl)-2,4,5,6,7,7a-hexahydro-1H-indole (**3.31h**): Synthesized according to general procedure C to yield pyrroline **3.31h** (93%, d.r.= >20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (d, *J* = 8.3, 2H), 7.54 (d, *J* = 8.2, 2H), 7.42 (d, *J* = 8.1, 2H), 7.22 (d, *J* = 8.0, 2H), 5.44 (d, *J* = 1.9, 1H), 5.11 (d, *J* = 1.7, 1H), 4.24 (dd, *J* = 8.2, 6.1, 1H), 2.60 – 2.53 (m, 1H), 2.43 (dd, *J* = 8.0, 6.0, 1H), 2.39 (s, 3H), 1.96 (t, *J* = 13.4, 1H), 1.85 (t, *J* = 12.4, 2H), 1.55 – 1.36 (m, 2H), 1.33 – 1.18 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 145.9, 143.7, 141.8, 135.6, 129.84 (q, *J* = 32.3), 129.8, 127.8, 127.7, 125.6 (q, *J* = 3.7), 124.4 (q, *J* = 272.1), 119.39, 70.1, 67.5, 37.4, 28.4, 26.7, 24.1, 21.7. **IR** (neat) 2936, 1618, 1448,, 1420, 1324, 1162, 1122, 1066, 1017, 827, 666, 591 cm^{-1}. **^{19}F NMR** (376.135 MHz, $CDCl_3$, C_6F_6) δ -65.64. **HRMS** (ESI) m/z 422.1417 [calculated mass for $C_{22}H_{23}F_3NO_2S$ ($M+H^+$) 422.1402].



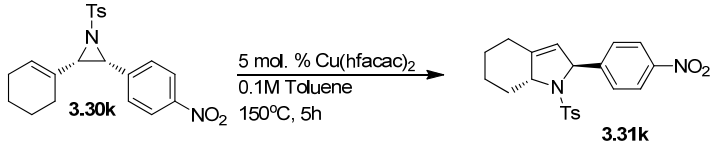
(2S,7aS)-2-(4-Nitrophenyl)-1-tosyl-2,4,5,6,7,7a-hexahydro-1H-indole (**3.31i**): Synthesized according to general procedure C to yield pyrroline **3.31i** (96%, d.r.= >20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.8, 2H), 7.64 (d, *J* = 8.3, 2H), 7.51 (d, *J* = 8.7, 2H), 7.28 (d, *J* = 8.9, 2H), 5.46 (d, *J* = 2.3, 1H), 5.10 (d, *J* = 1.8, 1H), 4.19 (dd, *J* = 9.8, 5.0, 1H), 2.62 – 2.53 (m, 1H), 2.46 – 2.42 (m, 1H), 2.42 (s, 3H), 2.03 – 1.79 (m, 3H), 1.56 – 1.37 (m, 2H), 1.31 – 1.18 (m, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 149.4, 147.4, 144.0, 142.5, 135.0, 129.9, 128.1, 127.8, 124.0, 118.8, 69.9, 67.6, 37.5, 28.3, 26.6, 24.1, 21.8. IR (neat) 2934, 1683, 1520, 1456, 1344, 1161, 1096, 772, 676, 658 593 cm^{-1}. HRMS (ESI) m/z 399.1380 [calculated mass for $C_{21}H_{23}N_2O_4S$ ($M+H^+$) 399.1379].



(2S,7aR)-1-Tosyl-2-(4-(trifluoromethyl)phenyl)-2,4,5,6,7,7a-hexahydro-1H-indole (**3.31j**): Synthesized according to general procedure C to yield pyrroline **3.31j** (92%, d.r.= >20:1).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.0, 2H), 7.12 – 7.08 (m, 4H), 6.96 (d, *J* = 7.9, 2H), 5.54 (dt, *J* = 5.0, 1.9, 1H), 5.23 (q, *J* = 1.9, 1H), 4.32 (dt, *J* = 10.2, 4.9, 1H), 2.93 – 2.84 (m, 1H), 2.57 – 2.49 (m, 1H), 2.31 (s, 3H), 2.16 – 2.01 (m, 1H), 1.91 – 1.79 (m, 2H), 1.55 – 1.32 (m, 2H), 1.25 (ddq, *J* = 12.2, 6.8, 4.1, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 143.5, 142.6, 142.5, 138.4, 130.00 (q, *J* = 32.2), 129.1, 128.9, 126.6, 125.1 (q, *J* = 3.8), 124.3 (q, *J* = 272.1), 119.6, 69.9, 67.1, 36.6, 28.7, 26.6, 24.0, 21.5. **IR** (neat) 2931, 1652, 1421, 1343, 1325, 1160, 1122, 1108, 1065, 1017, 837, 812, 660, 592 cm^{-1}. **^{19}F NMR** (376.135 MHz, $CDCl_3$, C_6F_6) δ -65.70. **HRMS** (ESI) m/z 422.1401 [calculated mass for $C_{22}H_{23}F_3NO_2S$ ($M+H^+$) 422.1402].

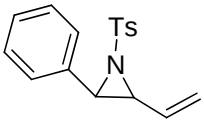


(2S,7aR)-2-(4-Nitrophenyl)-1-tosyl-2,4,5,6,7,7a-hexahydro-1H-indole (**3.31k**): Synthesized according to general procedure C to yield pyrroline **3.31k** (71%, d.r.= >20:1).

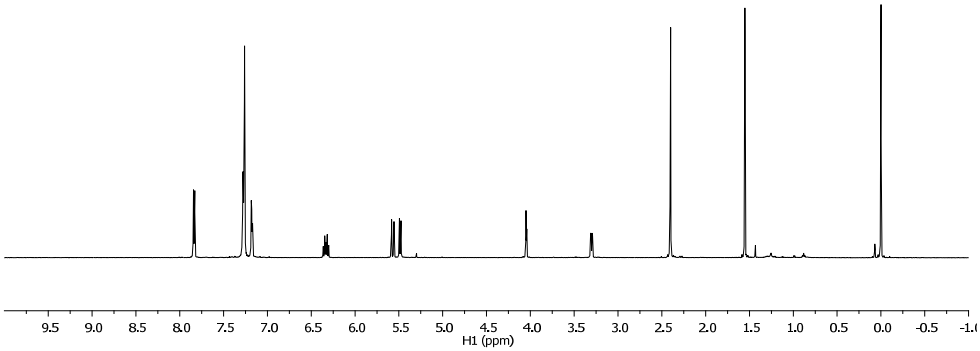
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, *J* = 8.8, 2H), 7.24 (d, *J* = 8.3, 2H), 7.21 (d, *J* = 8.8, 2H), 7.04 (d, *J* = 7.9, 2H), 5.57 (dt, *J* = 4.9, 1.8, 1H), 5.23 (d, *J* = 1.9, 1H), 4.38 (dd, *J* = 9.3, 4.9, 1H), 2.88 – 2.80 (m, 1H), 2.55 – 2.47 (m, 1H), 2.34 (s, 3H), 2.08 (td, *J* = 12.9, 3.9, 1H), 1.91 – 1.80 (m, 2H), 1.44 – 1.34 (m, 2H), 1.32 – 1.16 (m, 1H). **^{13}C**

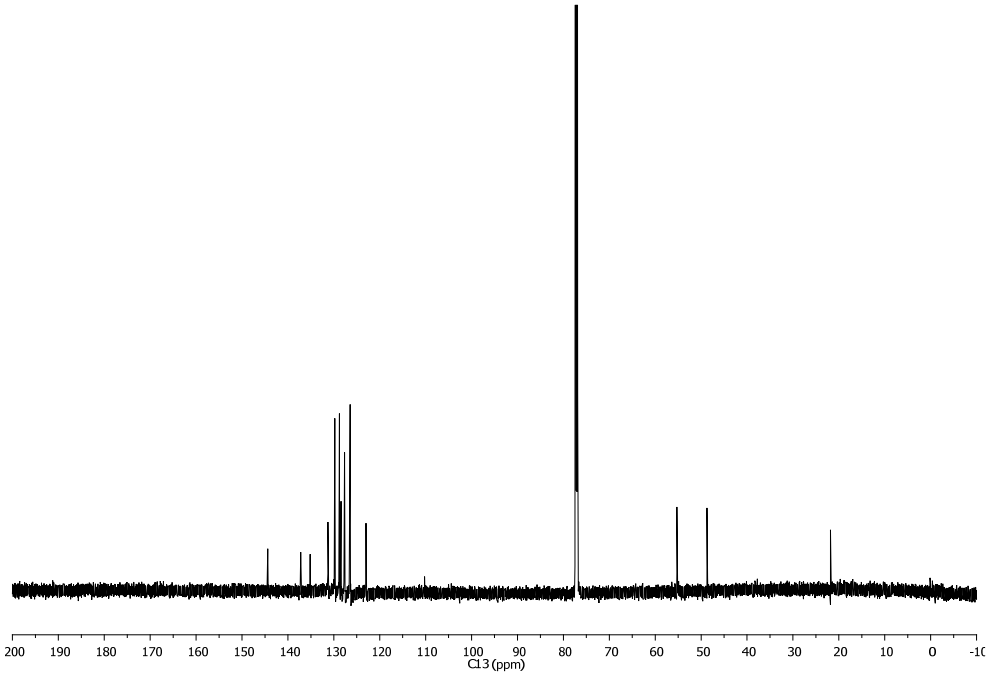
NMR (101 MHz, $CDCl_3$) δ 147.6, 147.5, 143.1(2), 143.0(7), 138.5, 129.3, 129.1, 126.8, 123.5, 119.2, 69.7, 67.3, 36.2, 28.6, 26.6, 23.9, 21.6. **IR** (neat) 2932, 1520, 1344, 1160, 1100, 668 cm^{-1}.

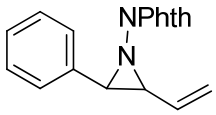
A3.2 ^{1}H and ^{13}C NMR Spectra for Chapter 3



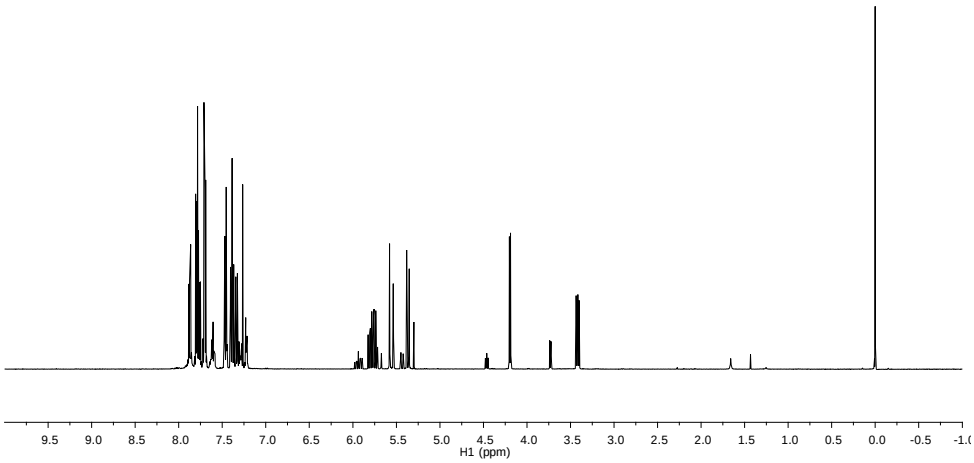
3.20a






NPhth
N

3.20b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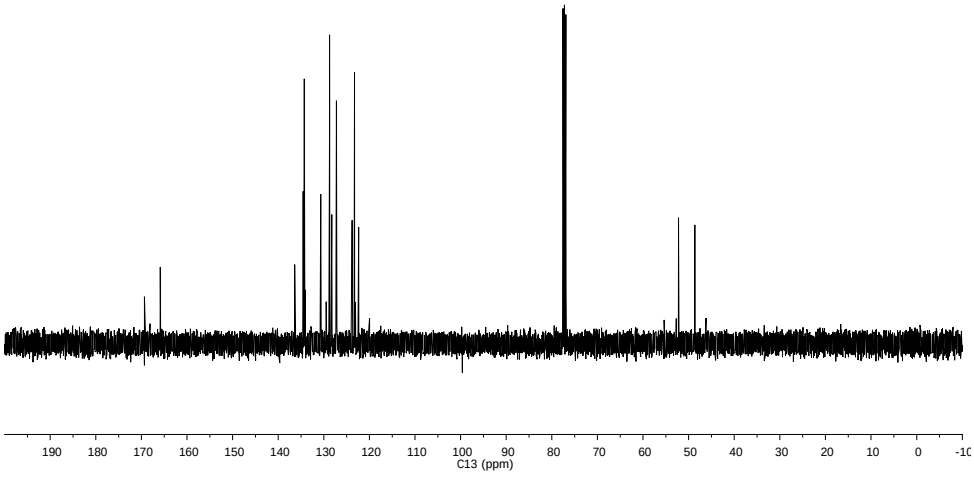
H1 (ppm)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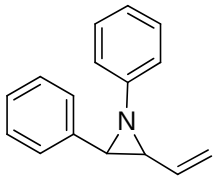
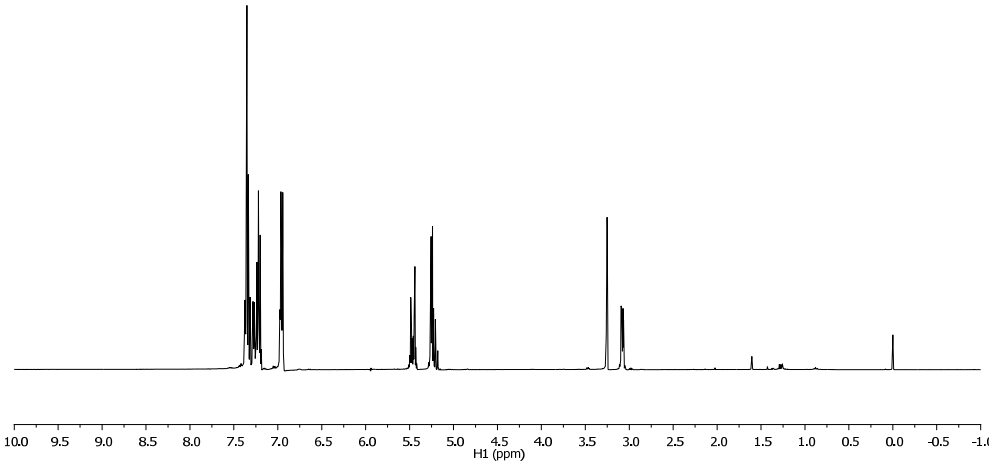
C13 (ppm)


N

3.20c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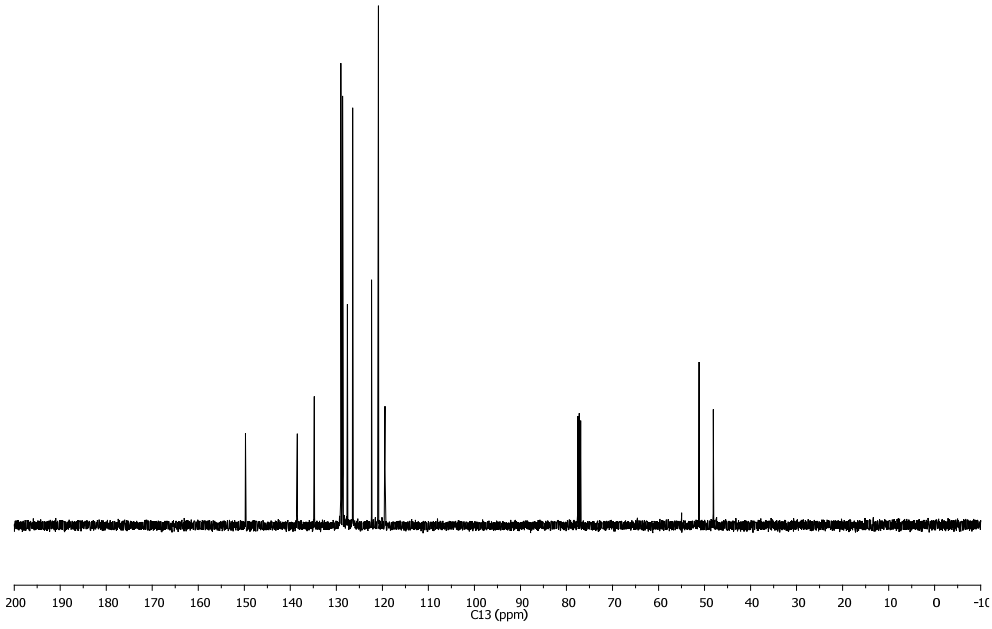
H1 (ppm)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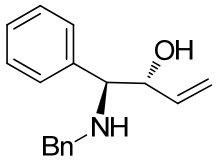
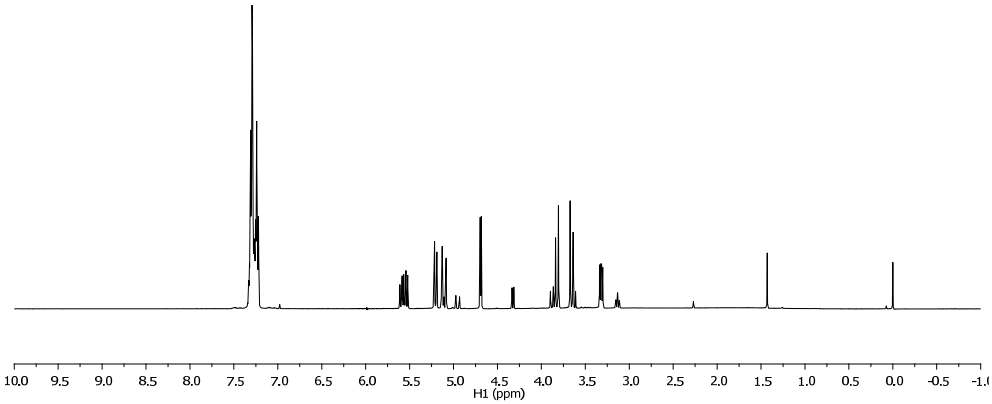
C13 (ppm)


OH
NH
Bn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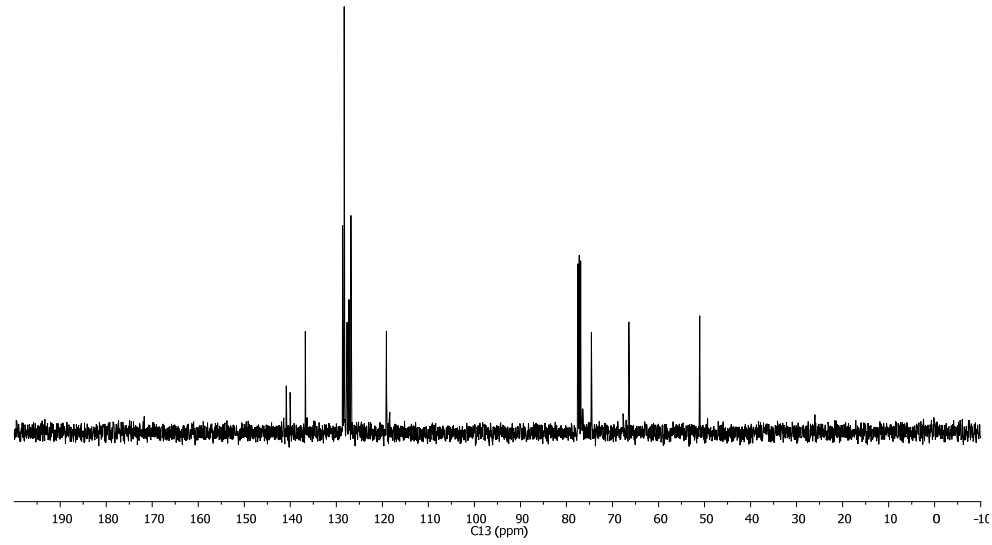
H1 (ppm)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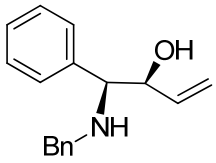
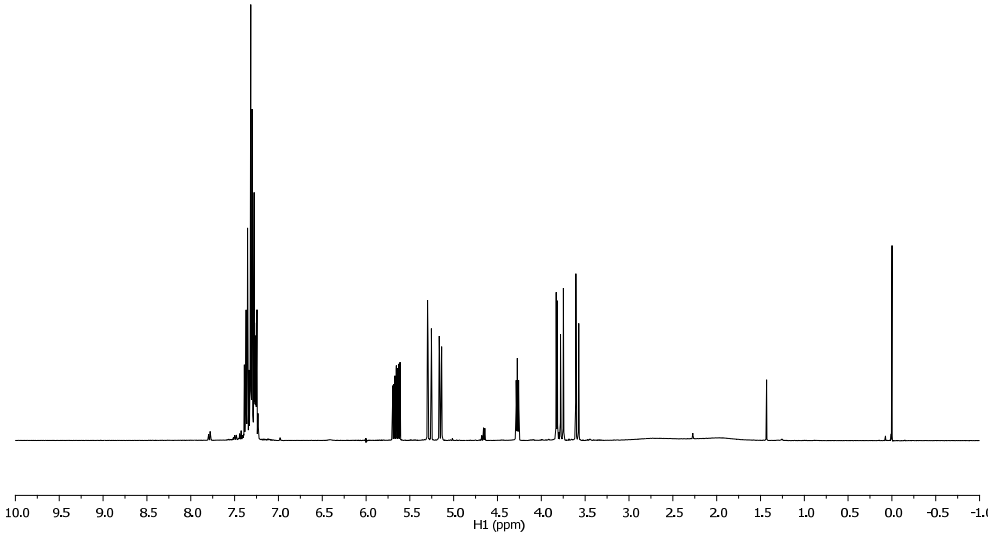
C13 (ppm)


OH
NH
Bn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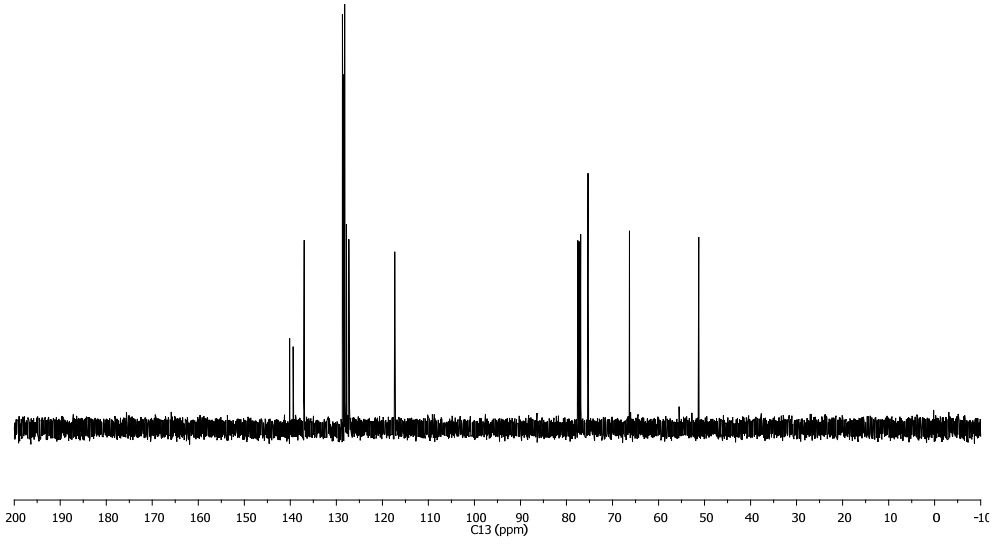
H1 (ppm)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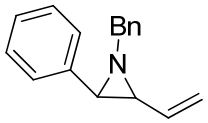
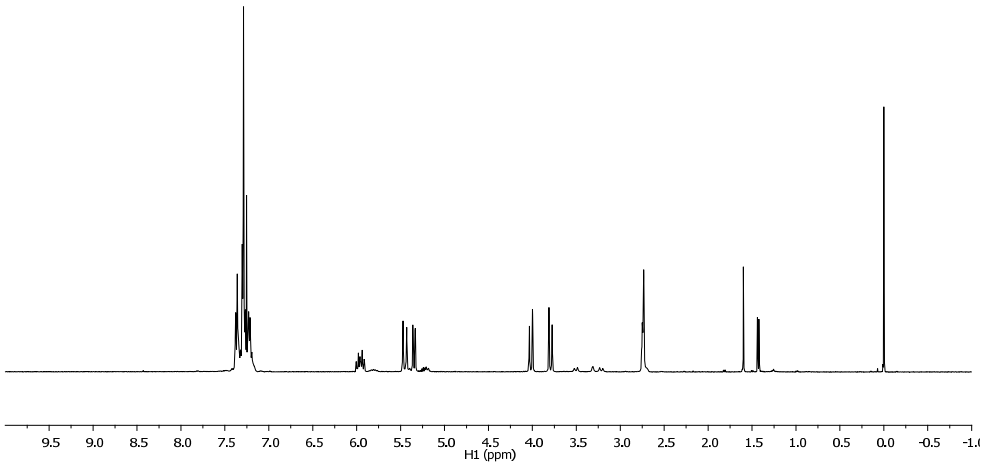
C13 (ppm)


Bn
N

3.20d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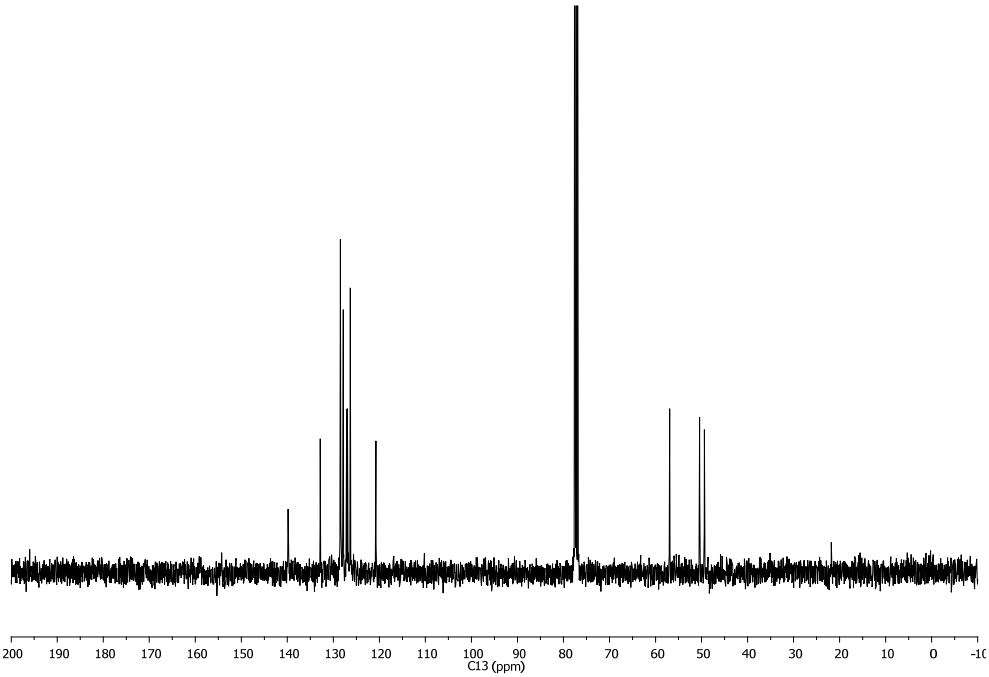
H1 (ppm)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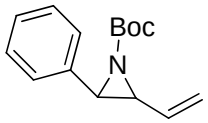
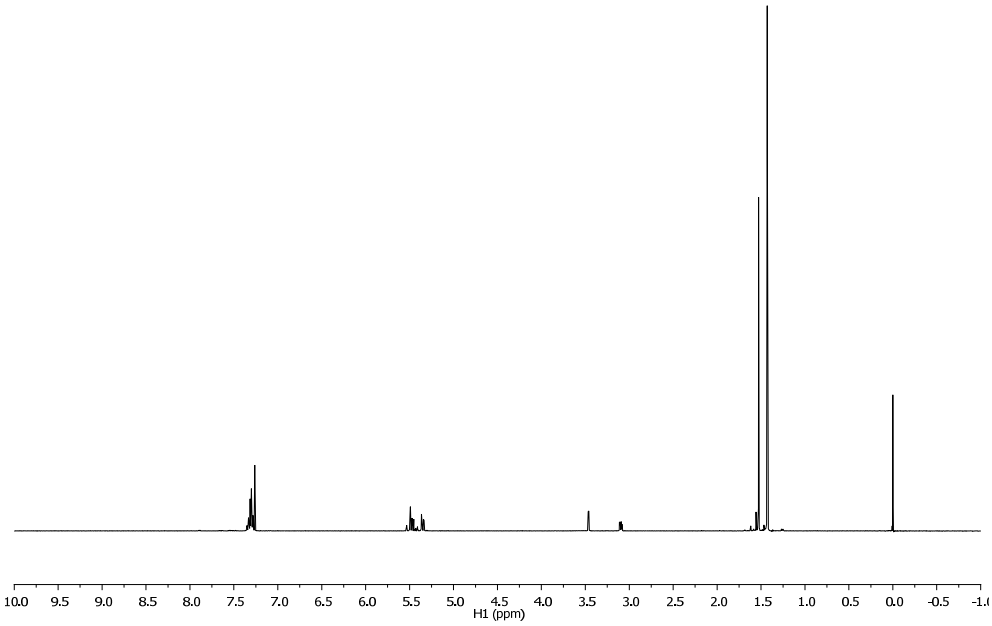
C13 (ppm)


Boc
N

3.20e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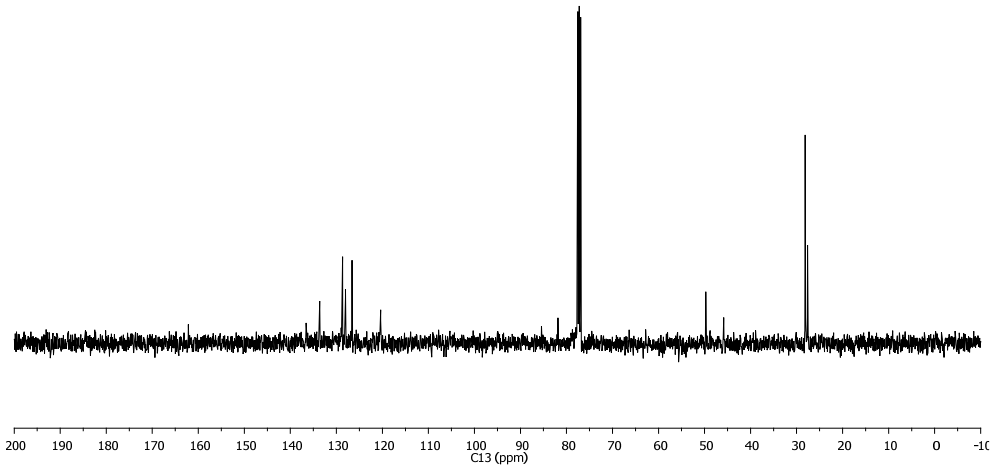
H1 (ppm)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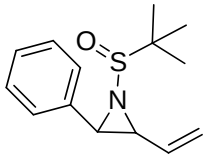
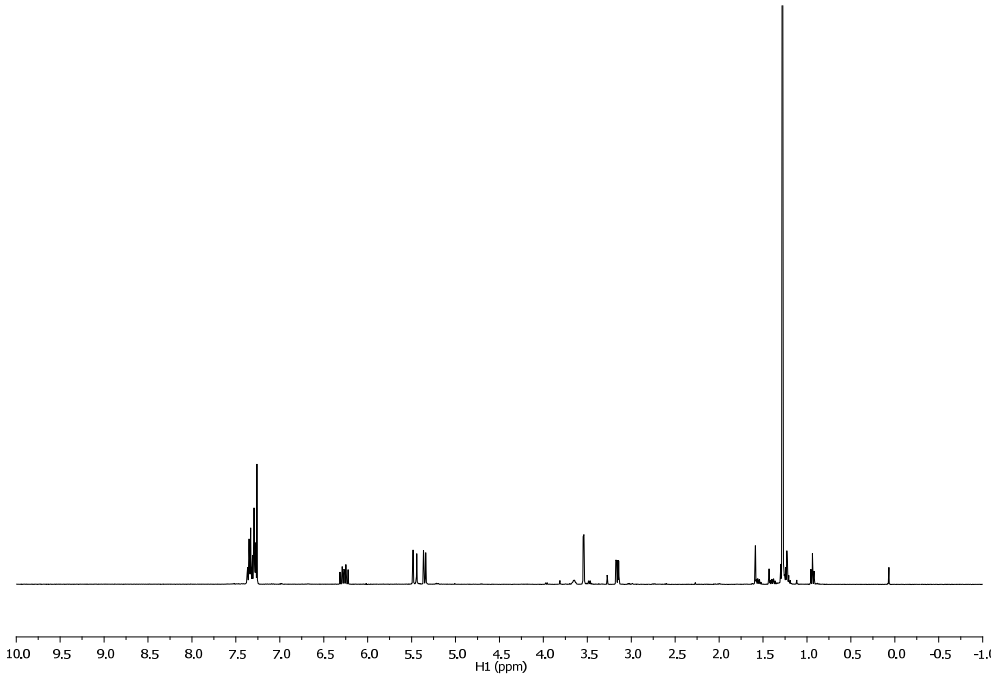
C13 (ppm)


O
S
N

3.20f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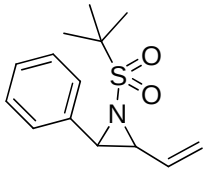
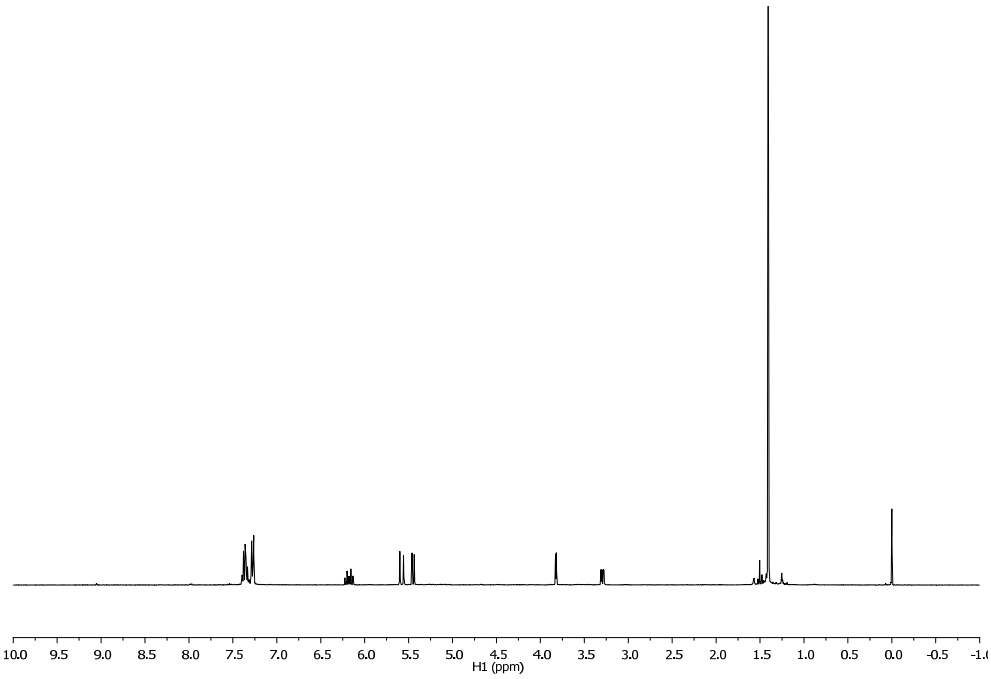
H1 (ppm)


O
S
O
N

3.20g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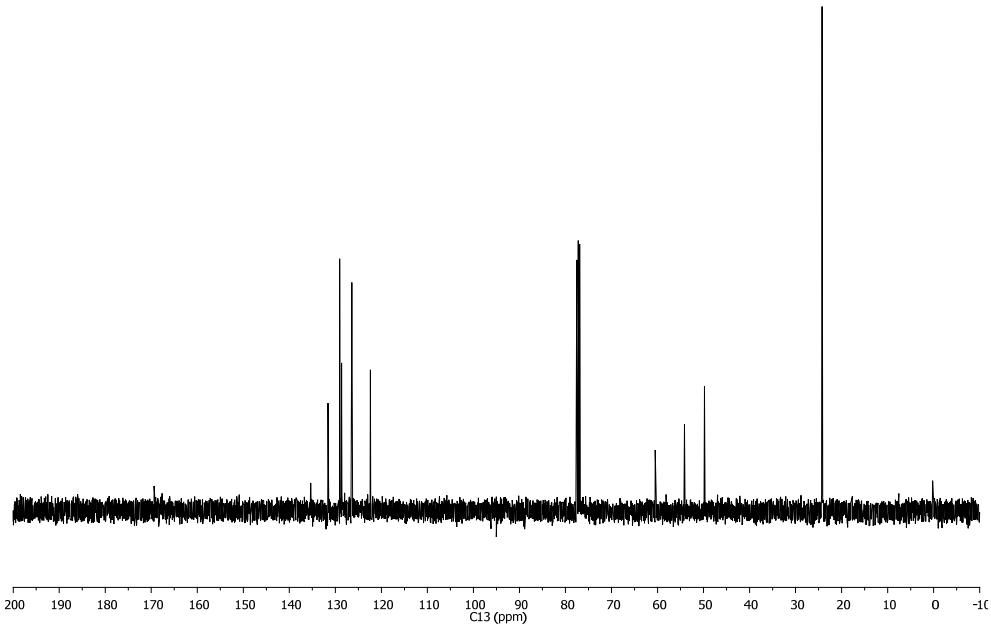
H1 (ppm)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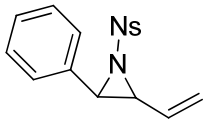
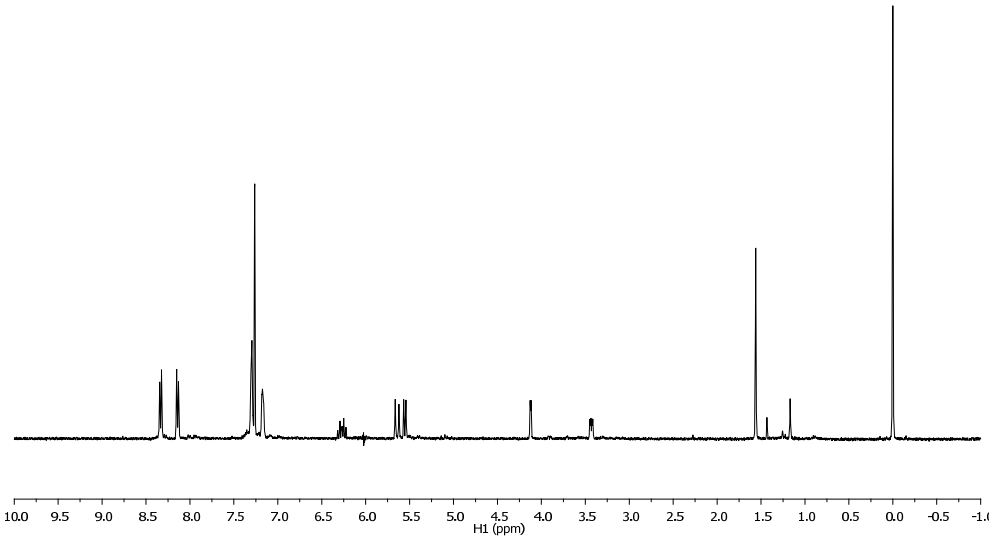
C13 (ppm)


Ns
N

3.20h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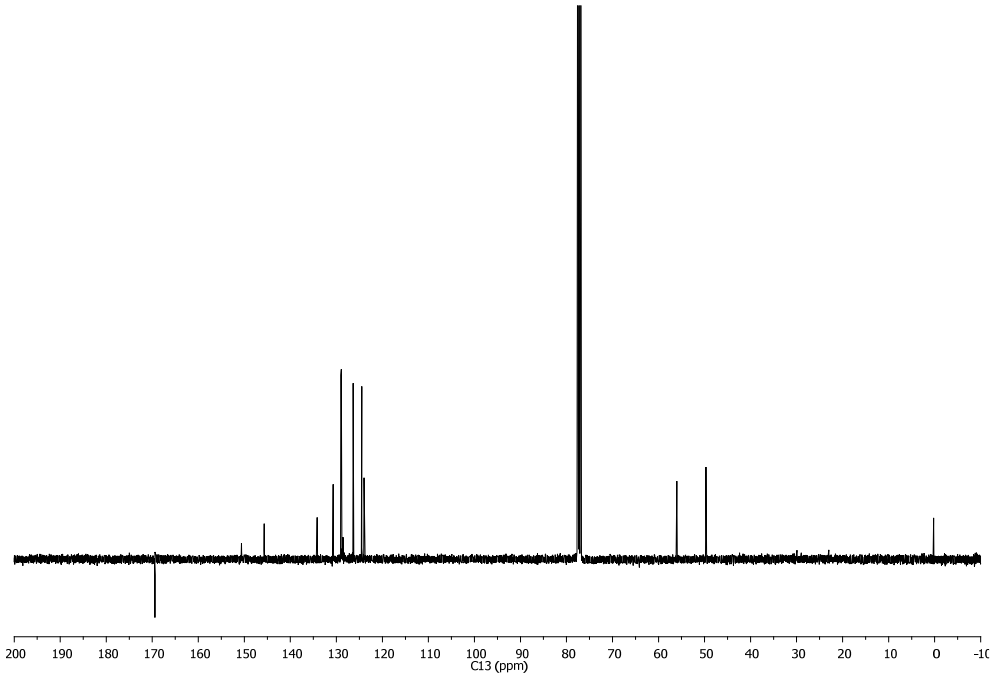
H1 (ppm)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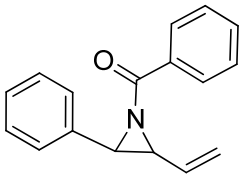
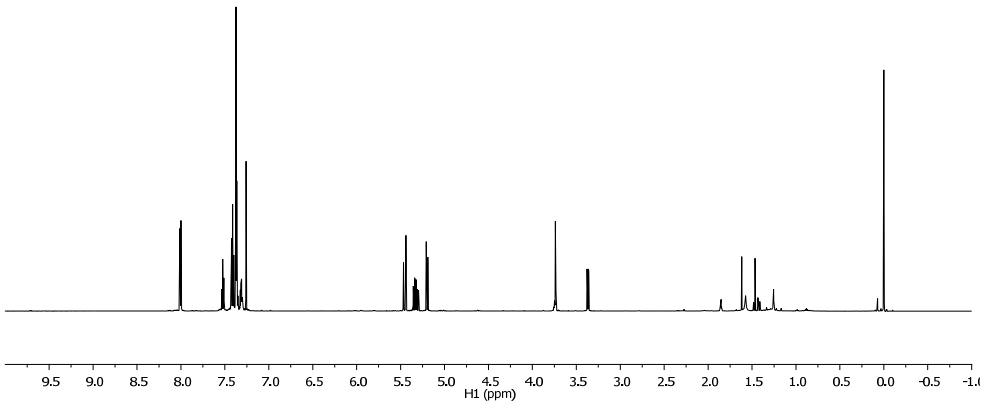

O
N

3.20j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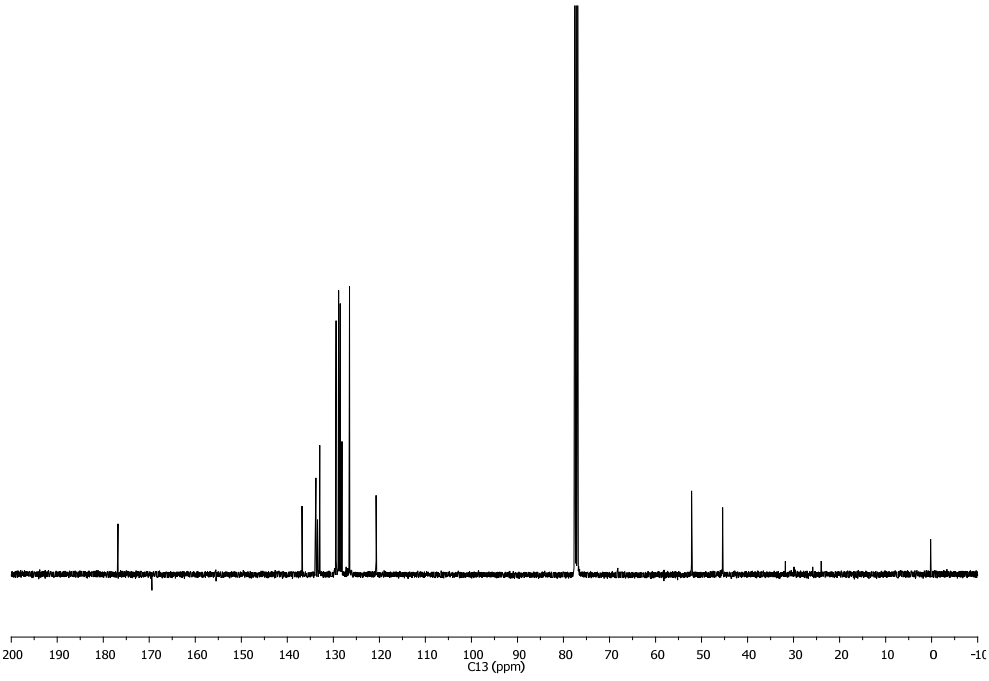
H1 (ppm)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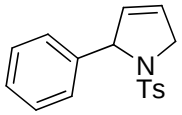
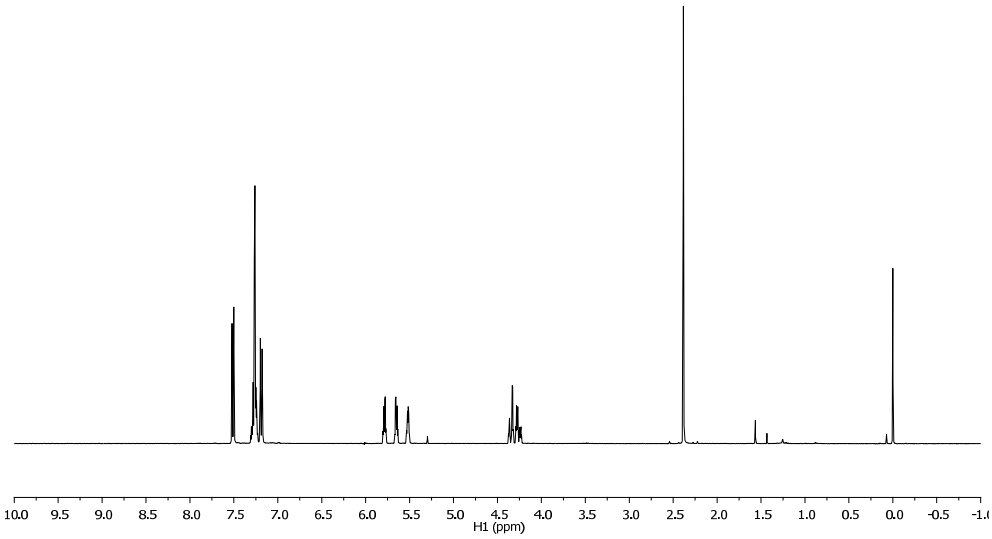

N
Ts

3.21a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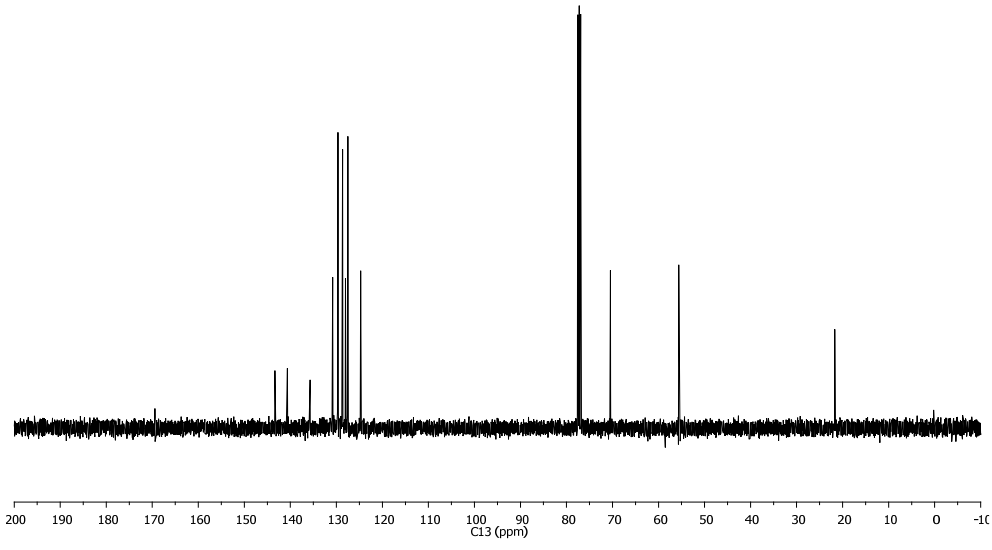
H1 (ppm)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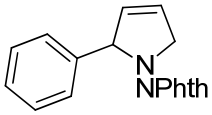
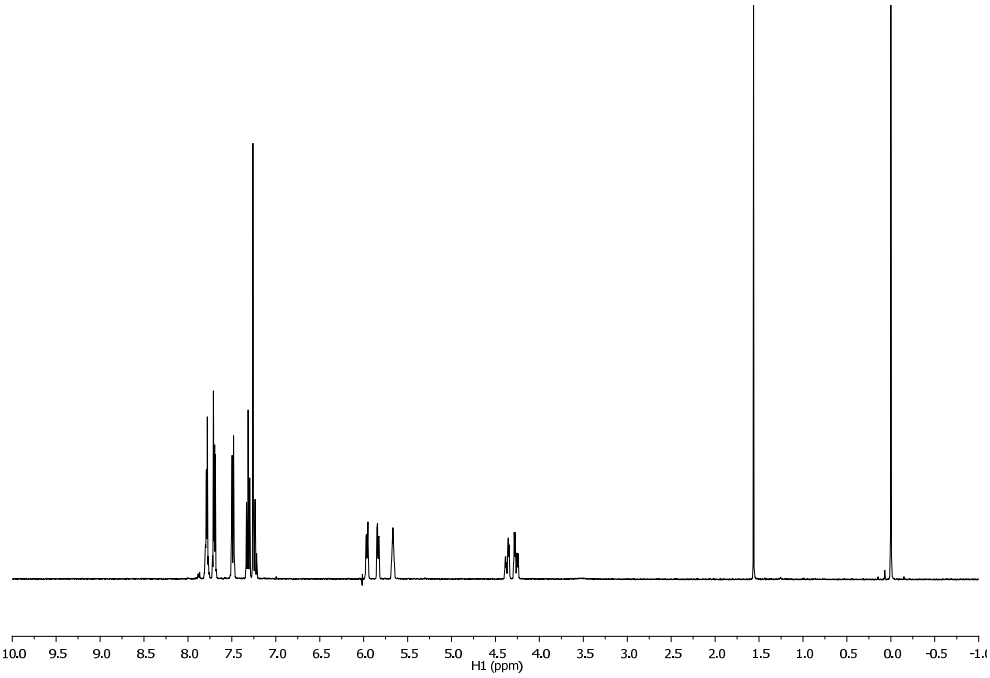
C13 (ppm)


N
NPhth

3.21b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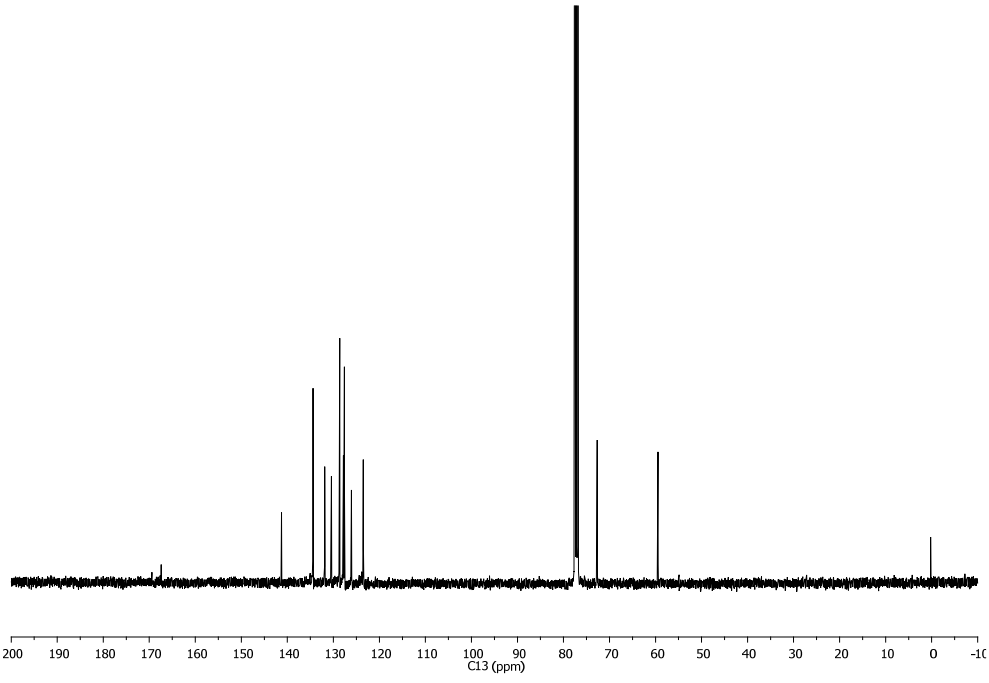
H1 (ppm)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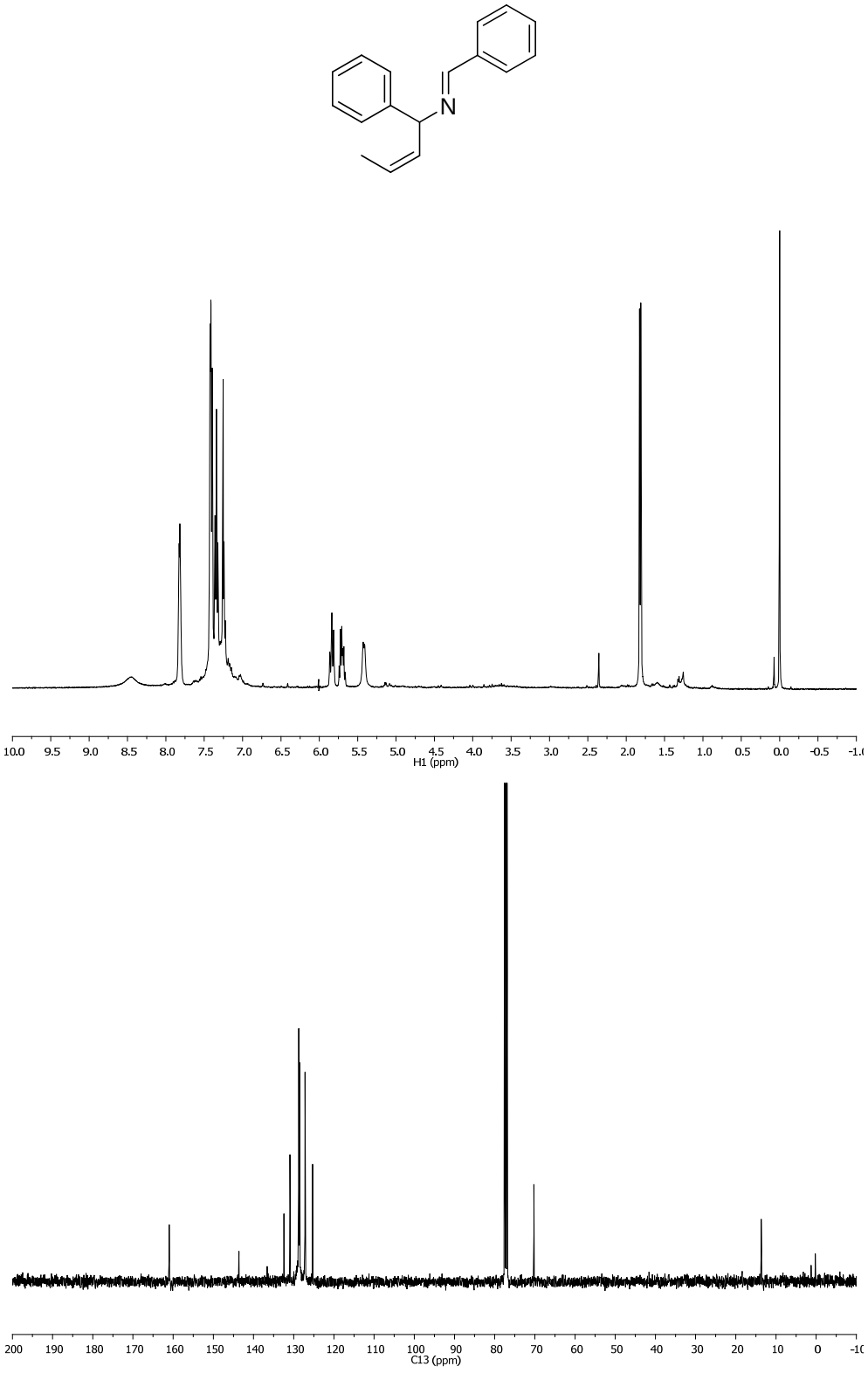
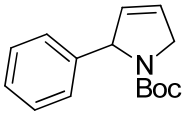
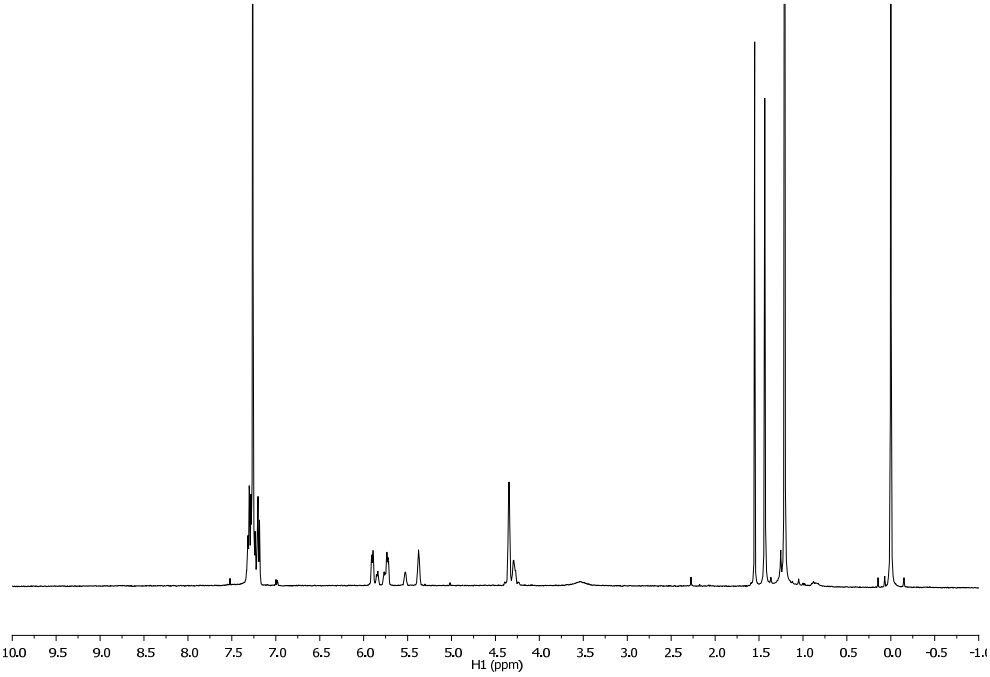

N
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
H1 (ppm)
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
C13 (ppm)


N
Boc

3.21e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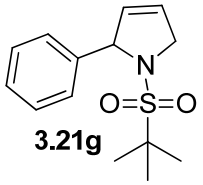
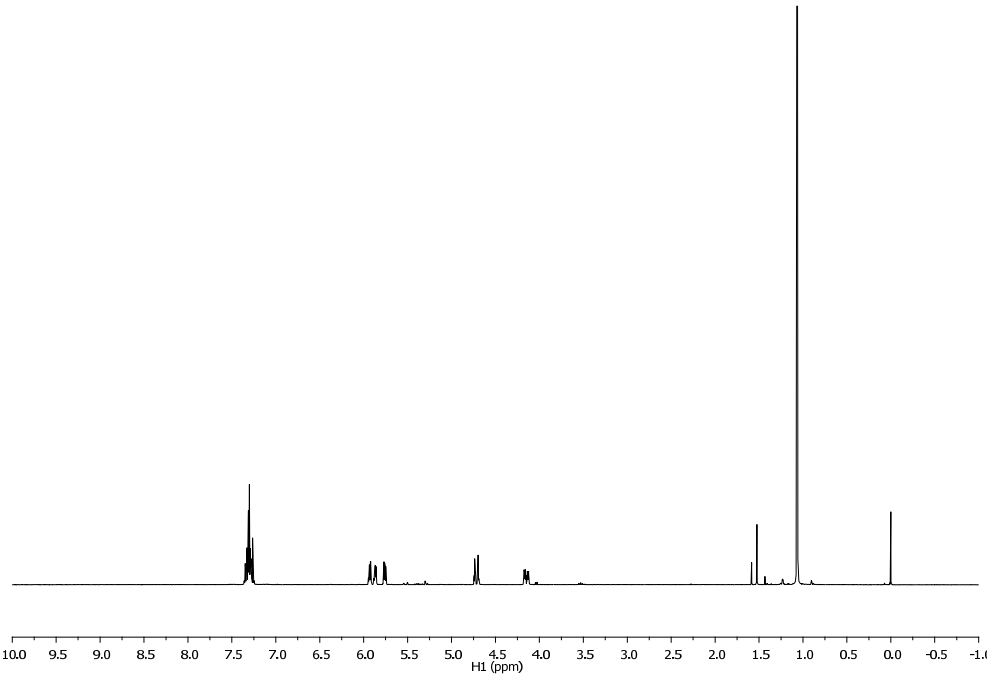
H1 (ppm)


N
O=S=O

3.21g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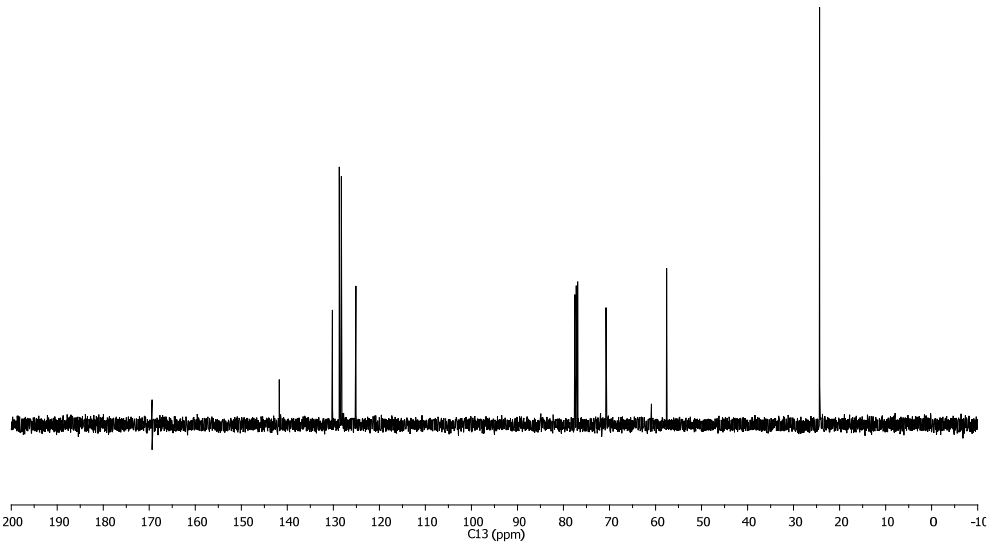
H1 (ppm)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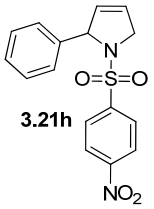
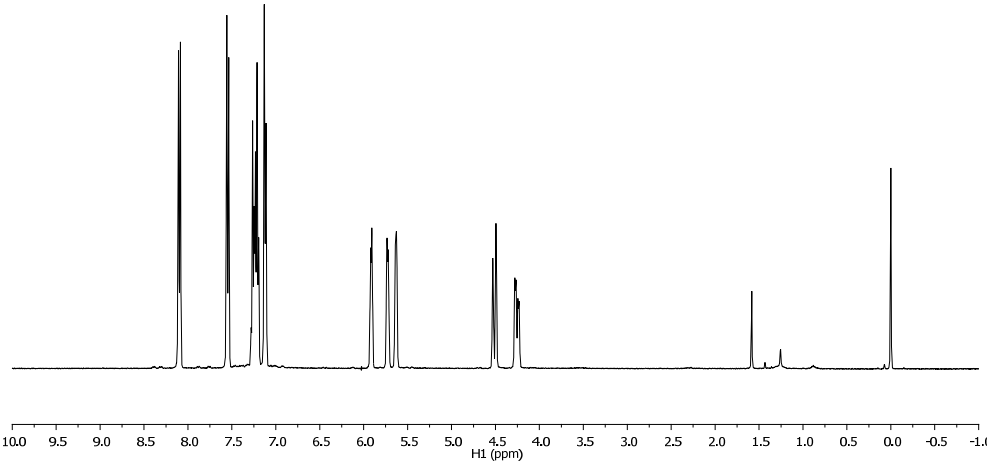
C13 (ppm)


N
O=S=O
NO2

3.21h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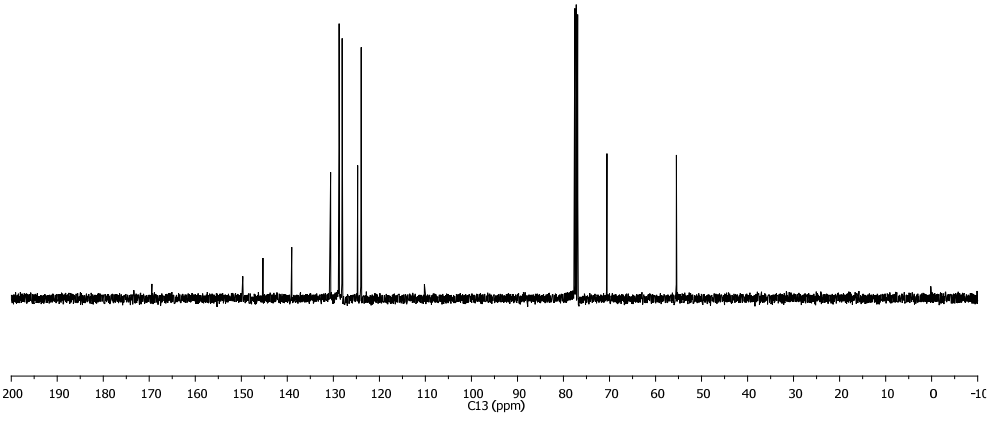
H1 (ppm)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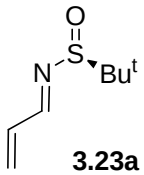
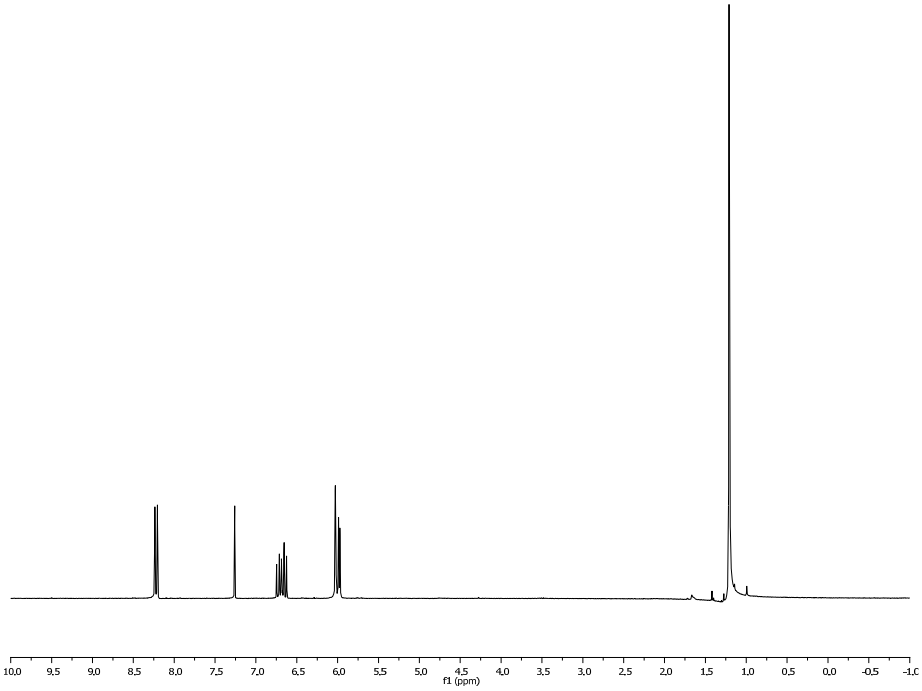
C13 (ppm)


O
S
N
Bu^t

3.23a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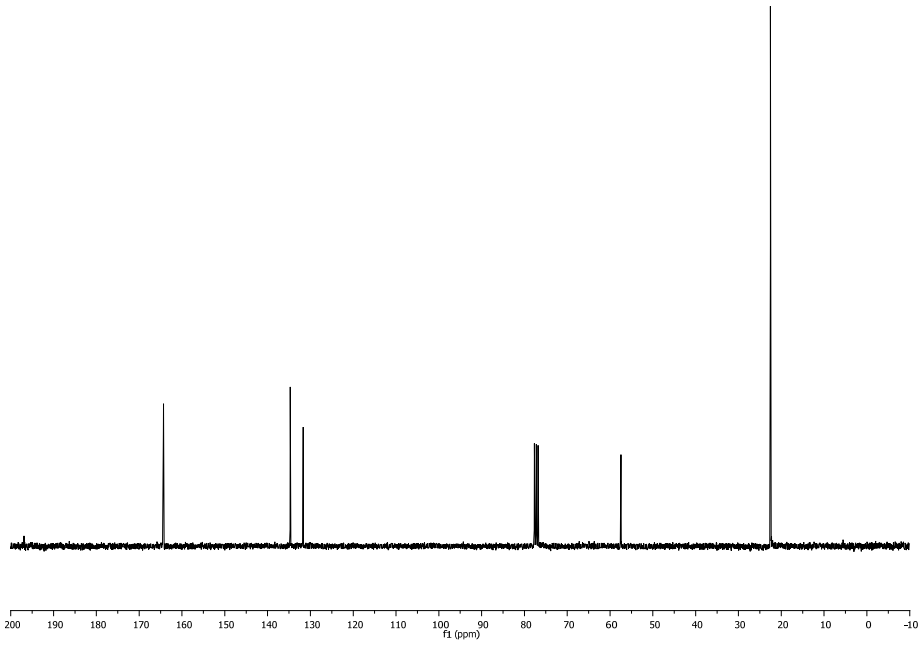
f1 (ppm)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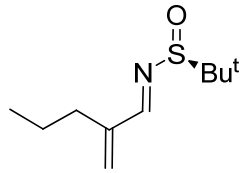
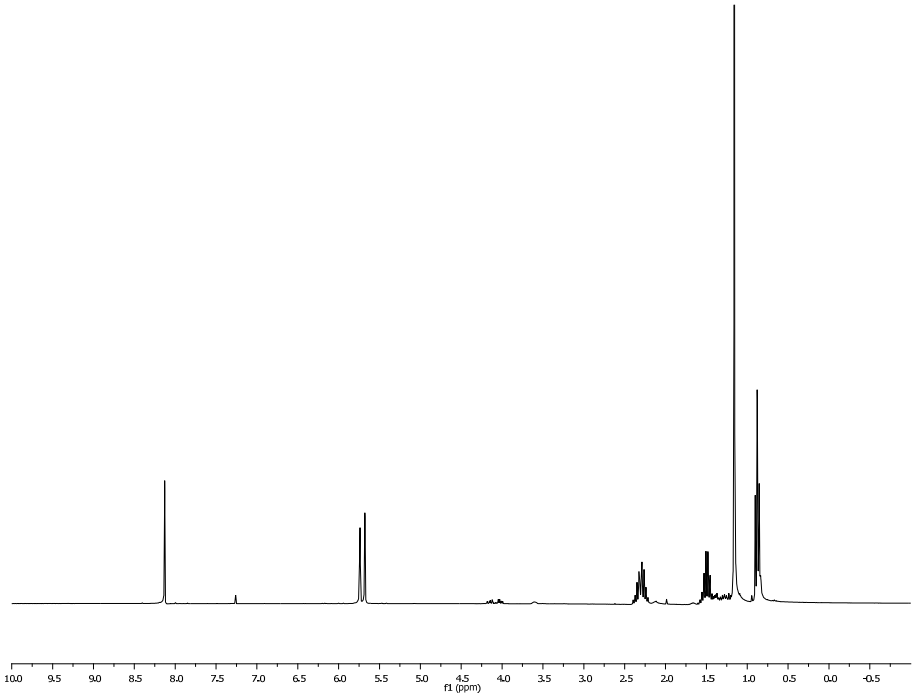
f1 (ppm)


O
S
N
Bu^t

3.23c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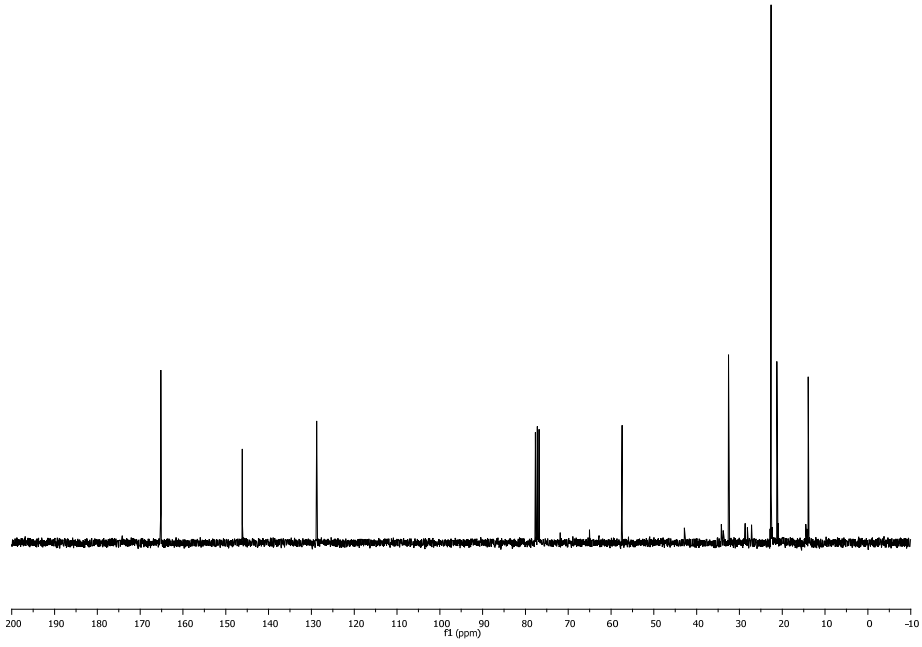
f1 (ppm)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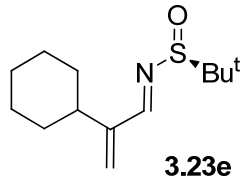
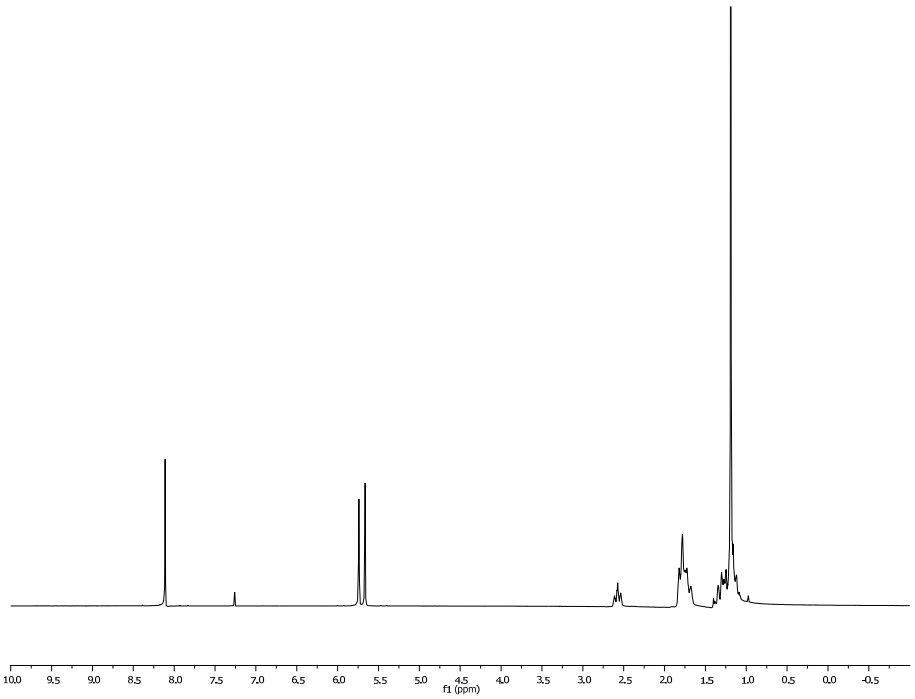
f1 (ppm)


O
S
N
Bu^t

3.23e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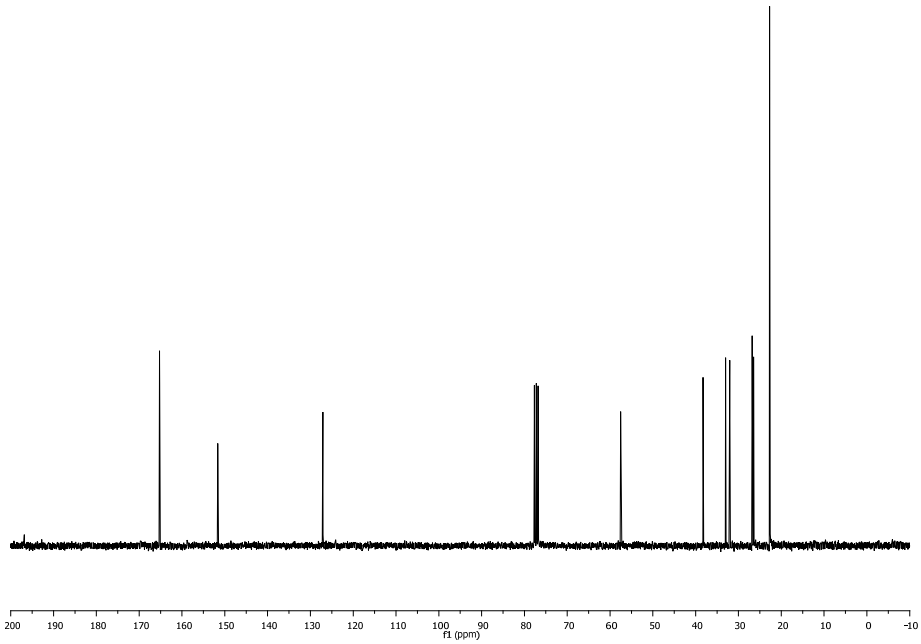
f1 (ppm)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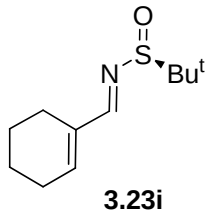
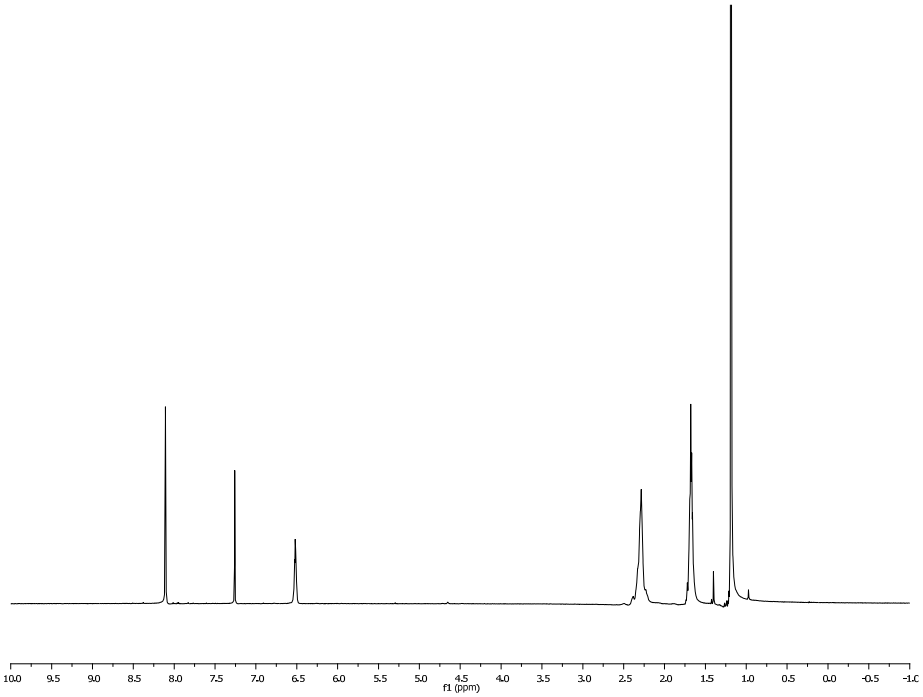
f1 (ppm)


O
S
N
Bu^t

3.23i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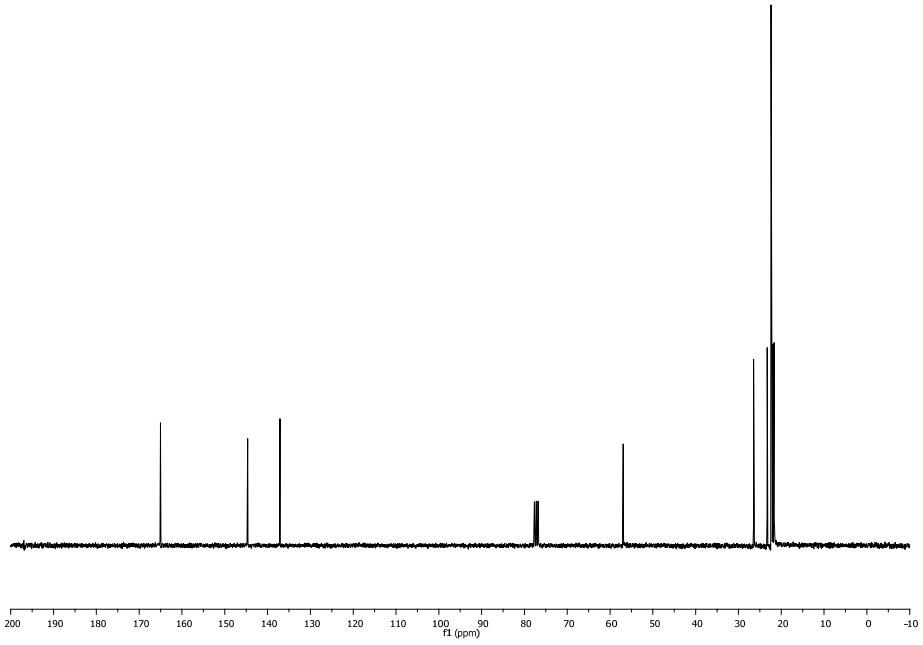
f1 (ppm)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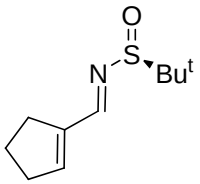
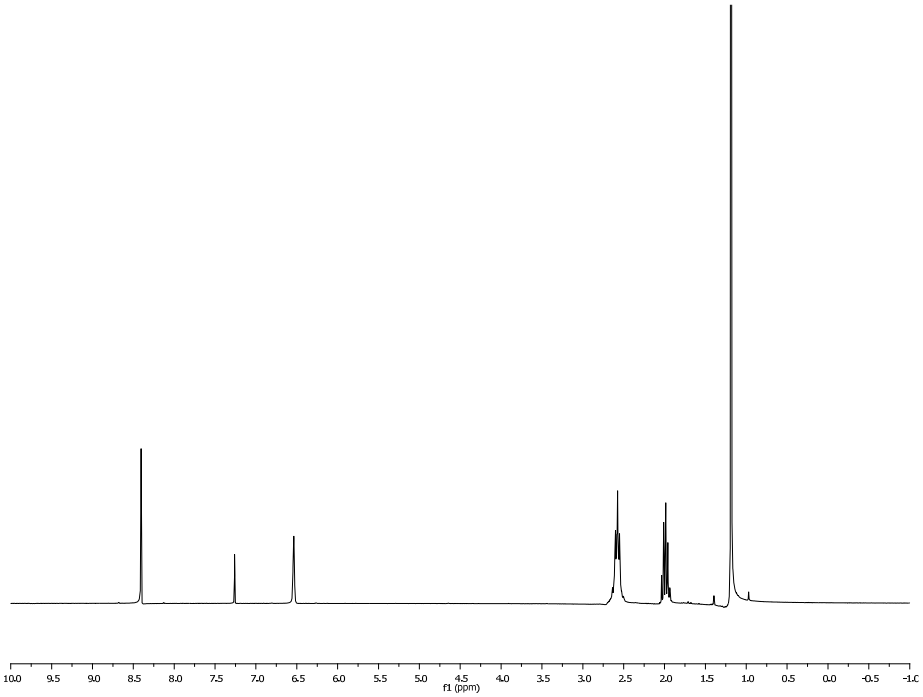
f1 (ppm)


O
S
N
Bu^t

3.23k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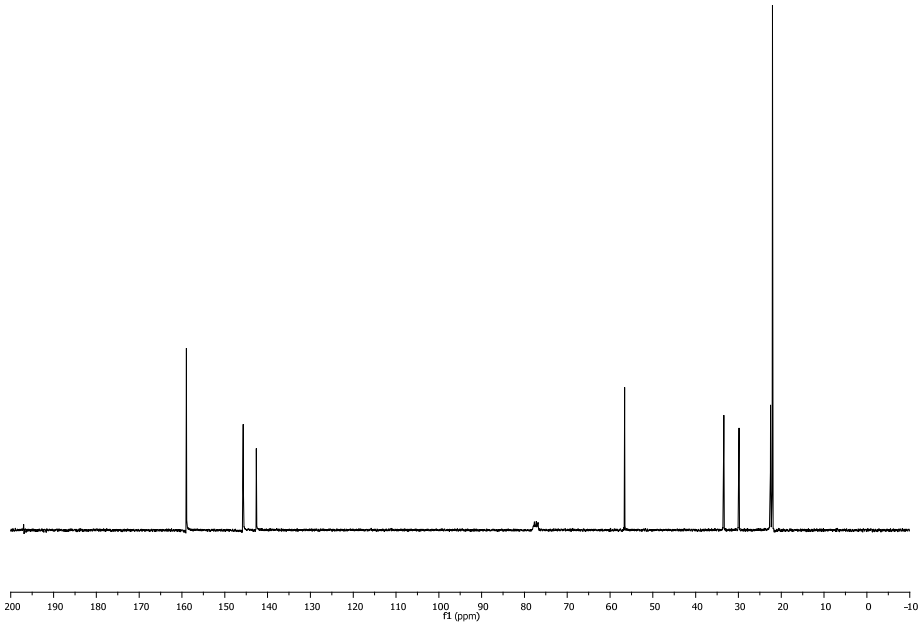
f1 (ppm)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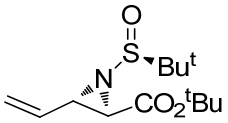
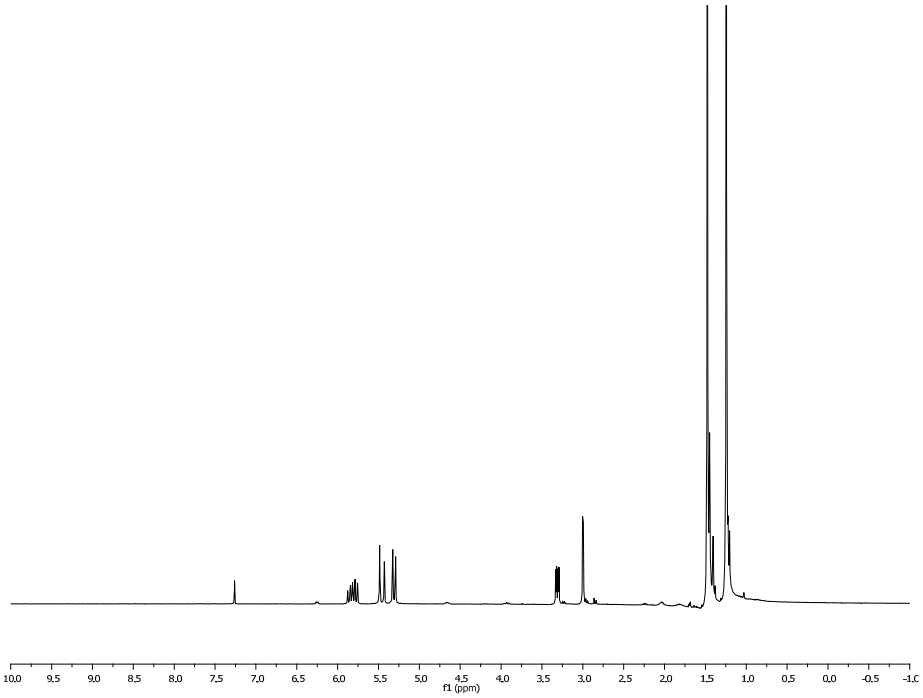
f1 (ppm)


O
S
Bu^t
N
CO2tBu

3.26a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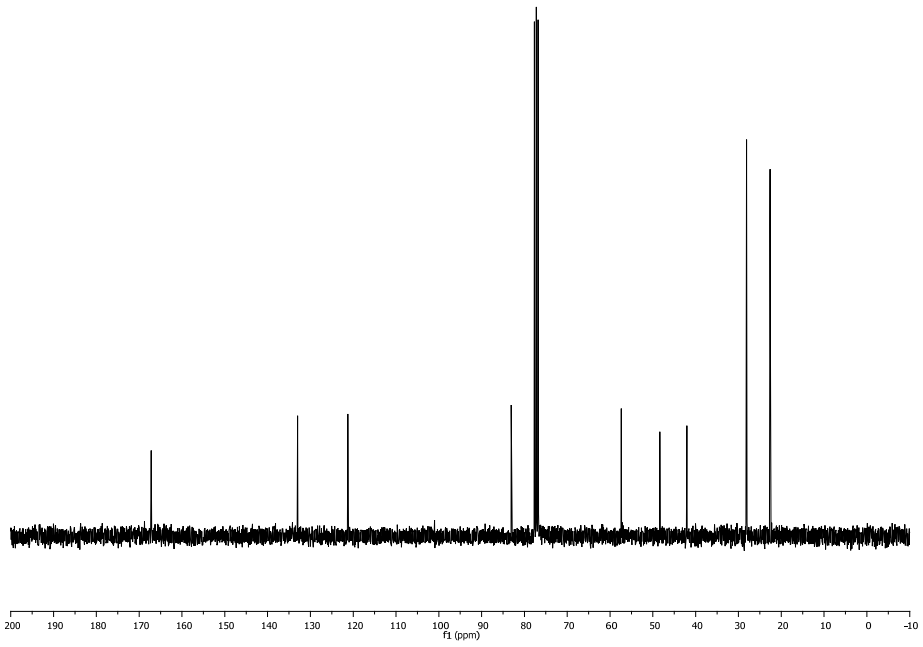
f1 (ppm)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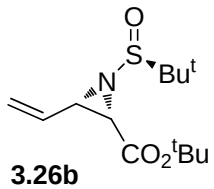
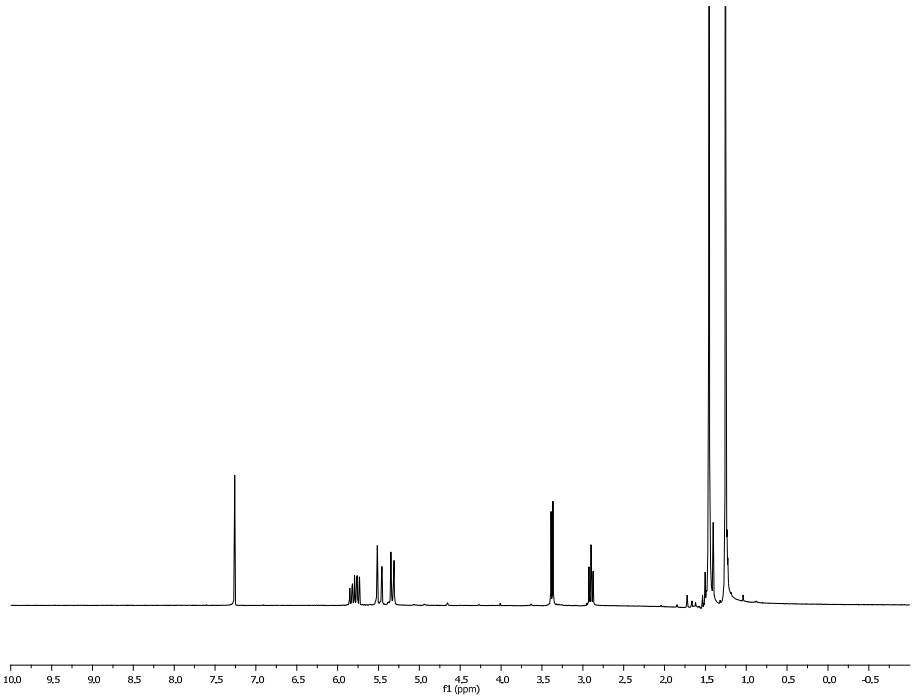
f1 (ppm)


O
S
N
Bu^t
CO2^tBu

3.26b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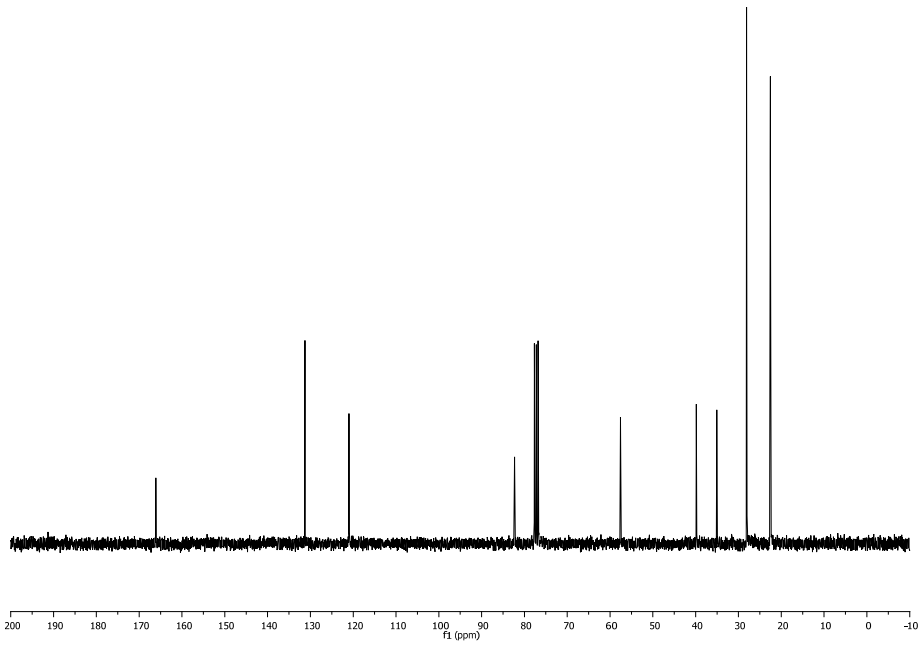
f1 (ppm)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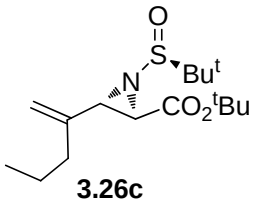
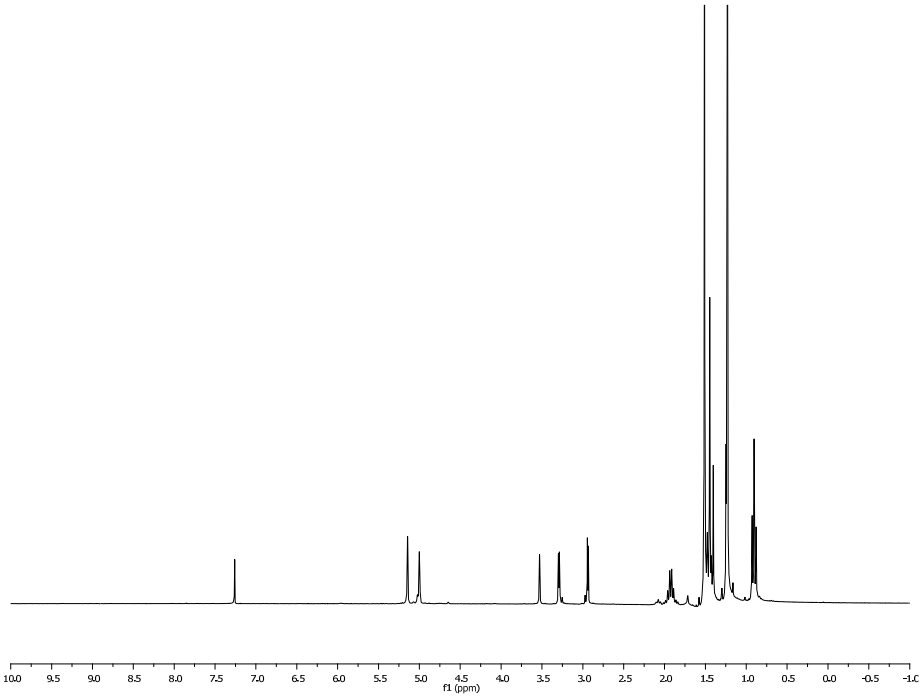
f1 (ppm)


O
S
Bu^t
N
CO2tBu

3.26c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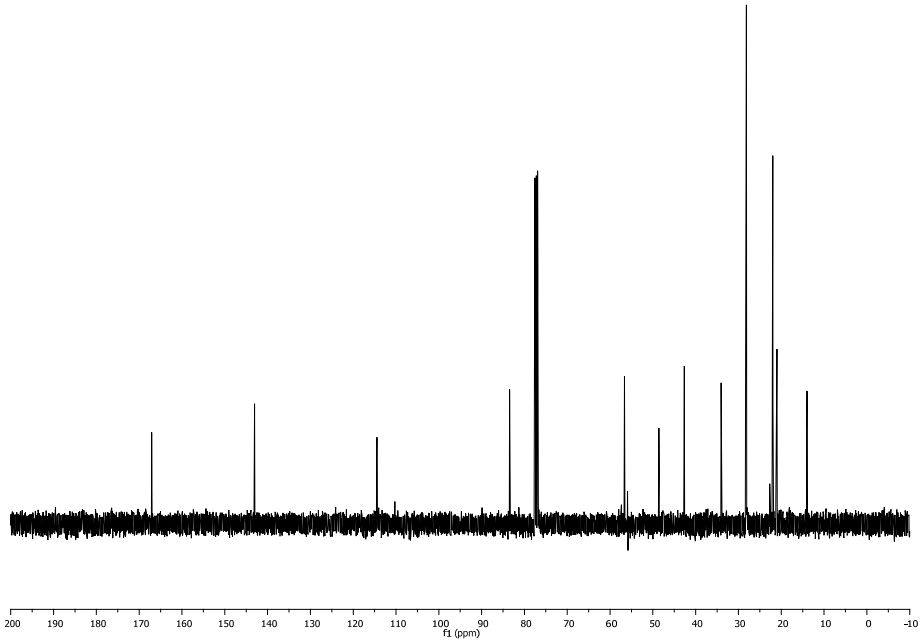
f1 (ppm)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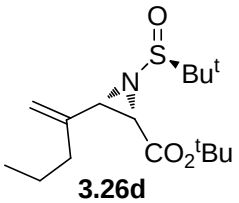
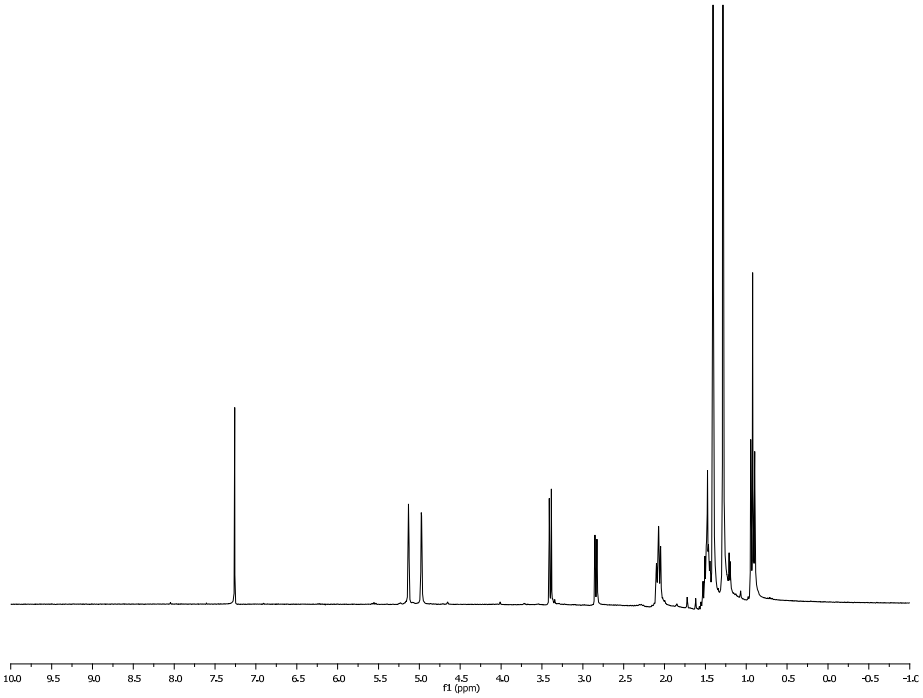
f1 (ppm)


O
S
N
Bu^t
CO2^tBu

3.26d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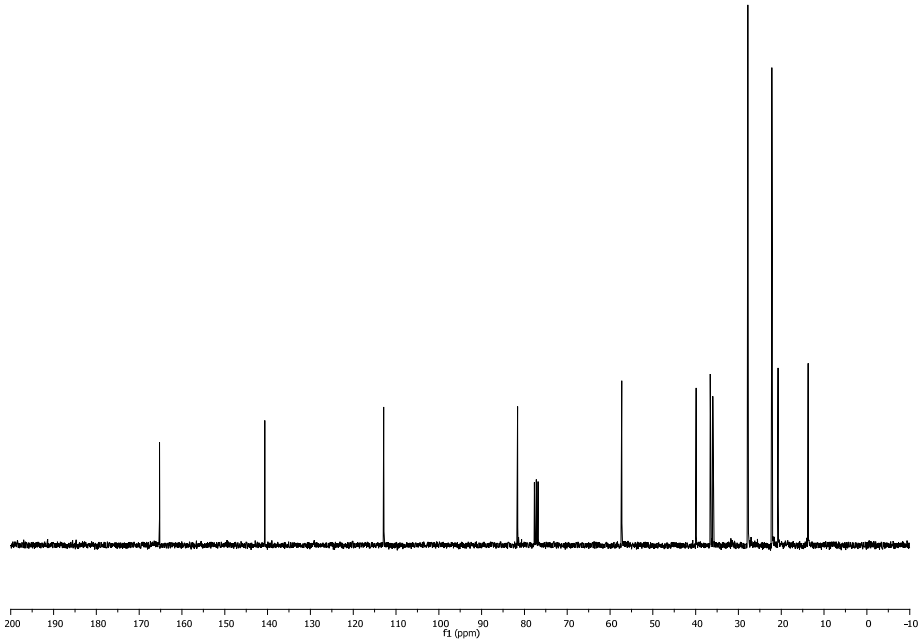
f1 (ppm)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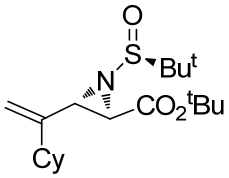
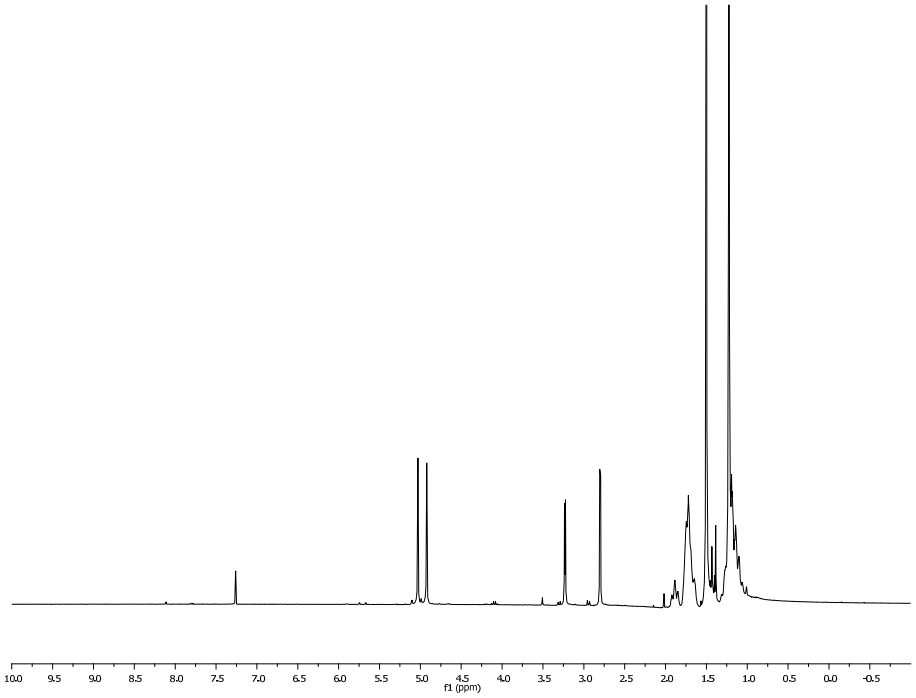
f1 (ppm)


O
S
Bu^t
N
CO2tBu
Cy

3.26g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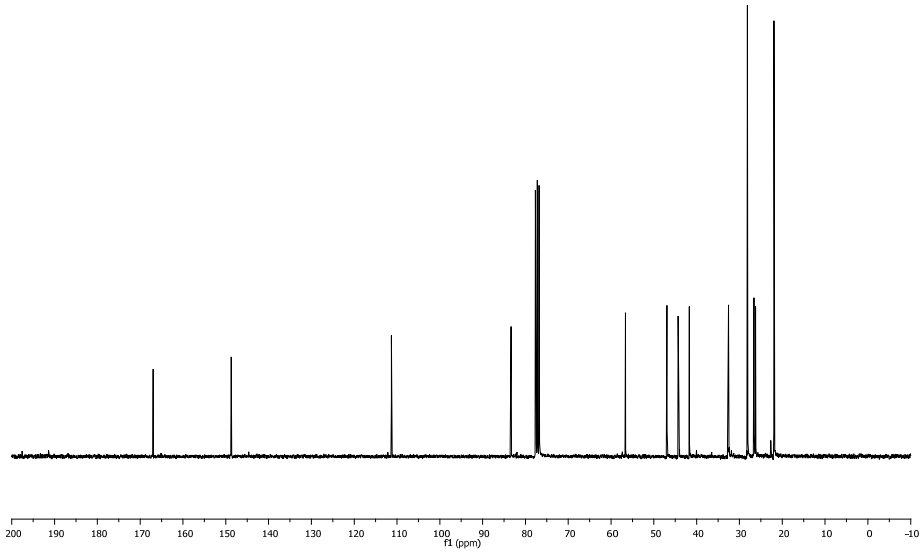
f1 (ppm)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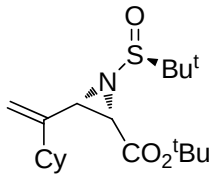
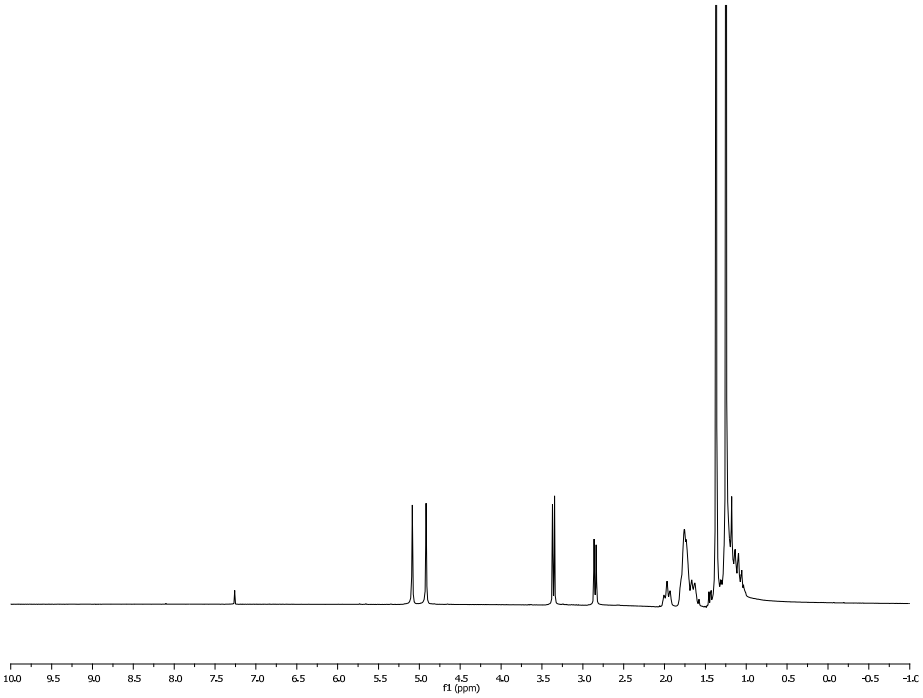
f1 (ppm)


O
S
Bu^t
N
Cy
CO2tBu

3.26f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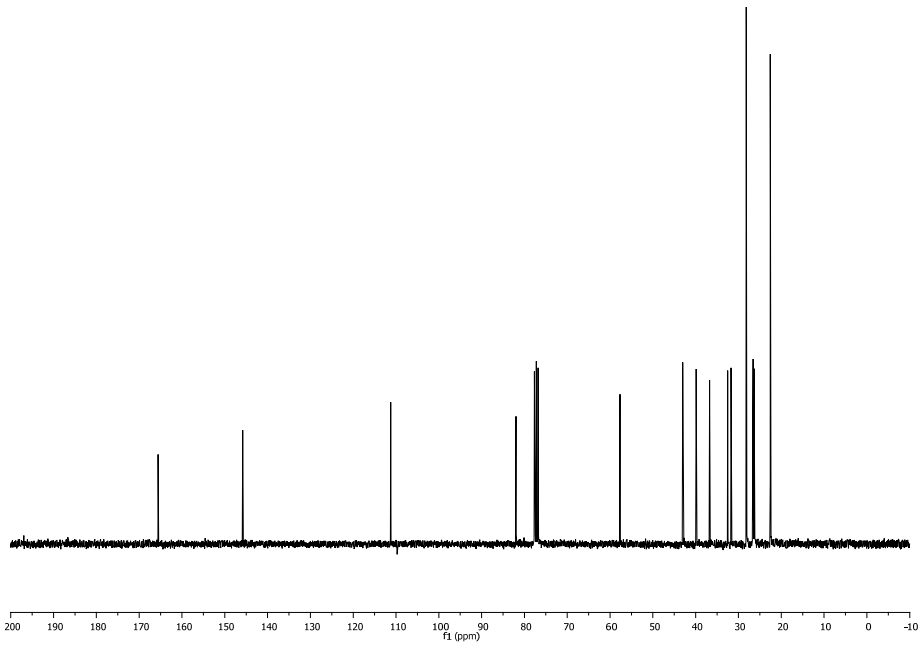
f1 (ppm)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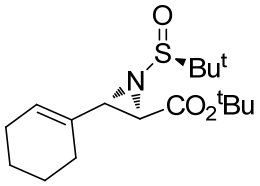
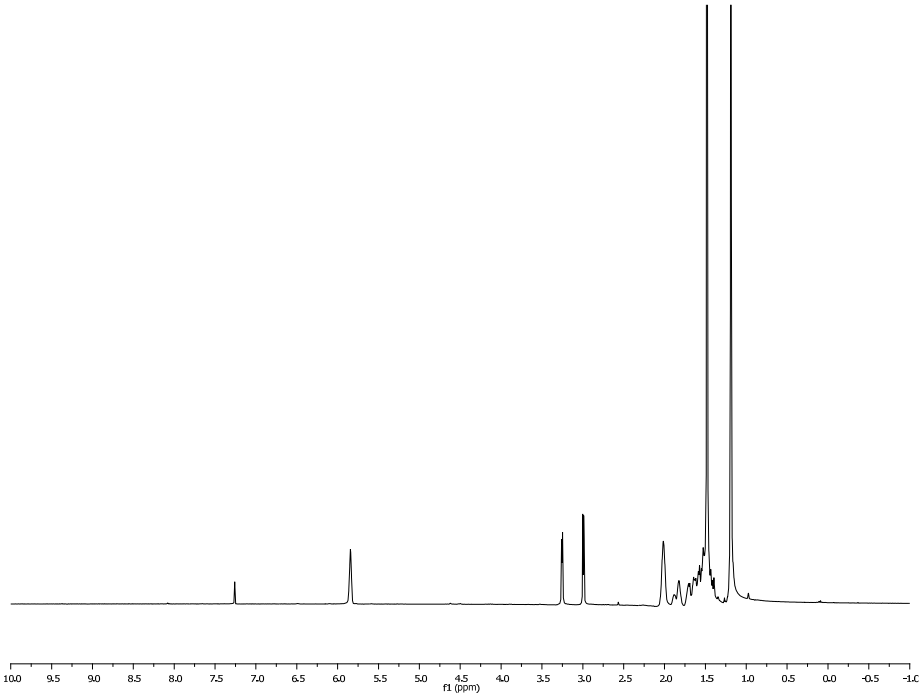
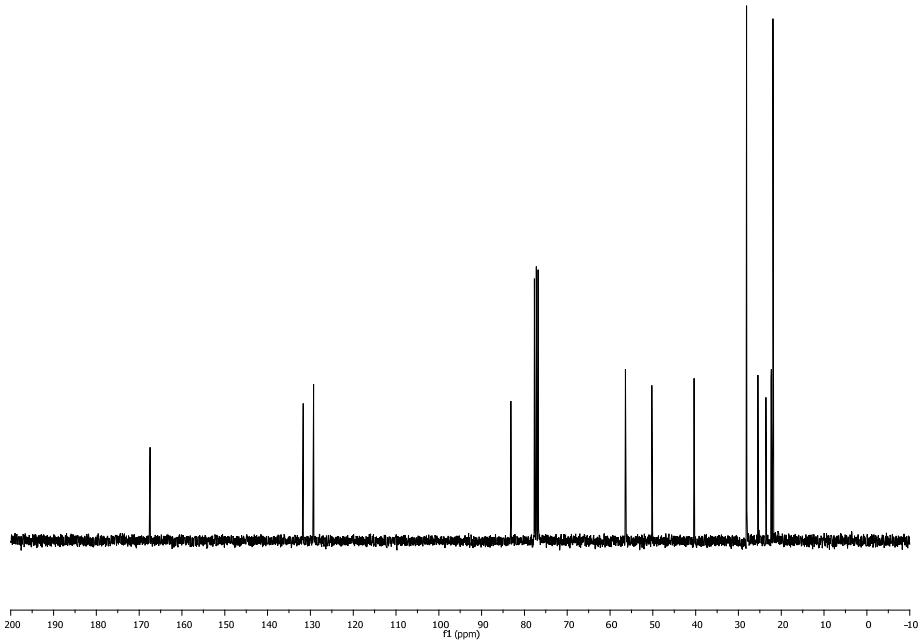
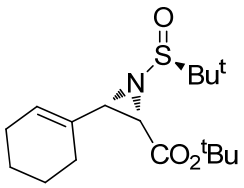


3.26i







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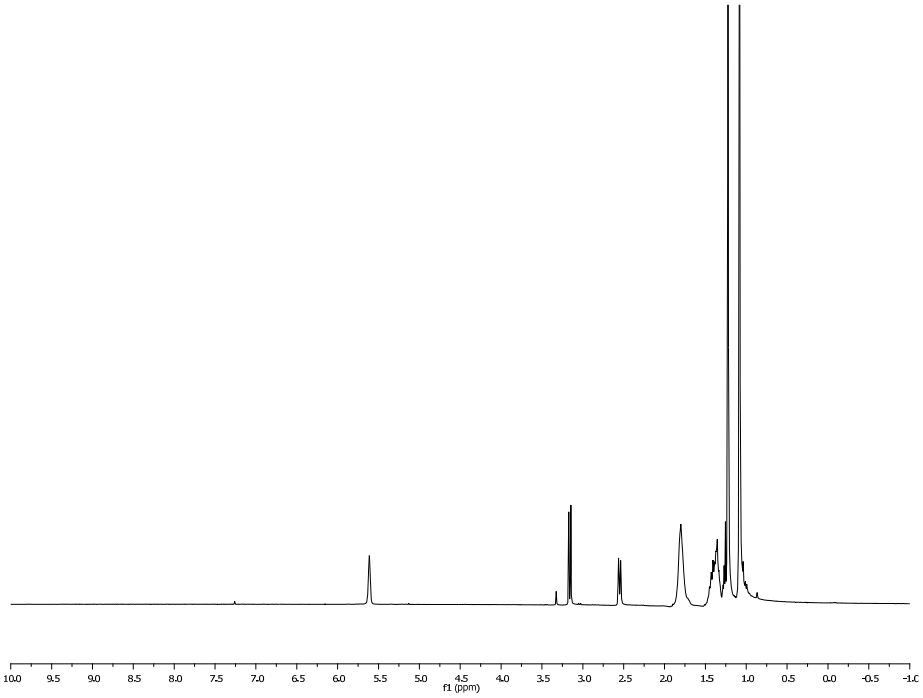
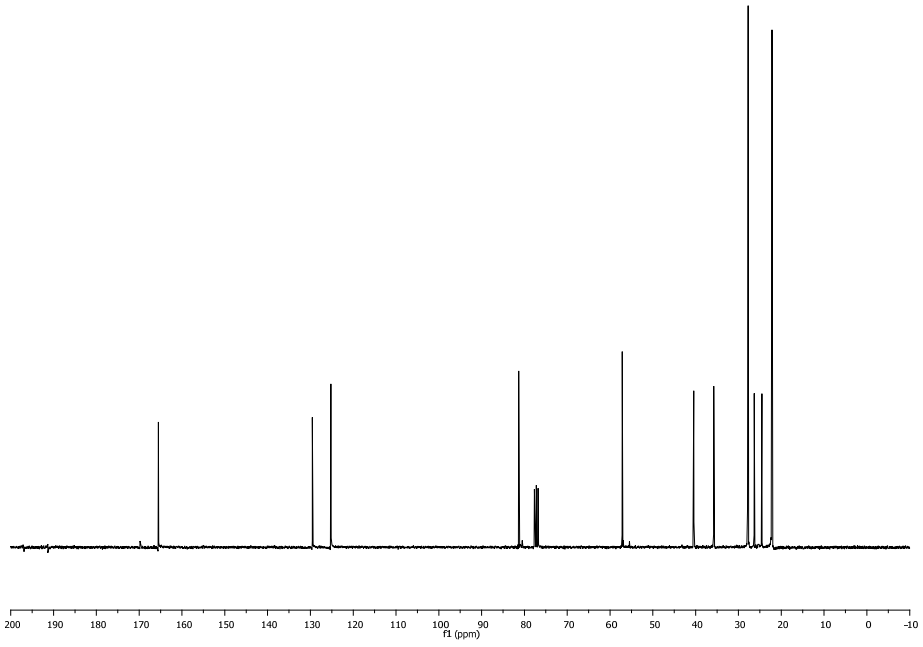
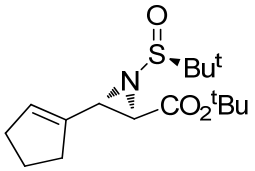
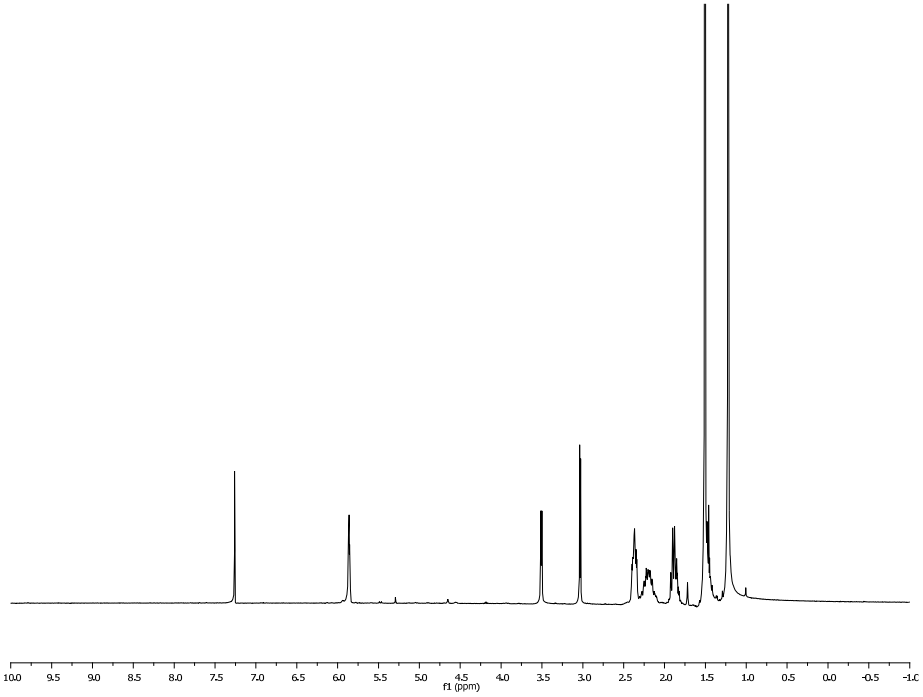





O
S
Bu^t
N
CO2tBu

3.26k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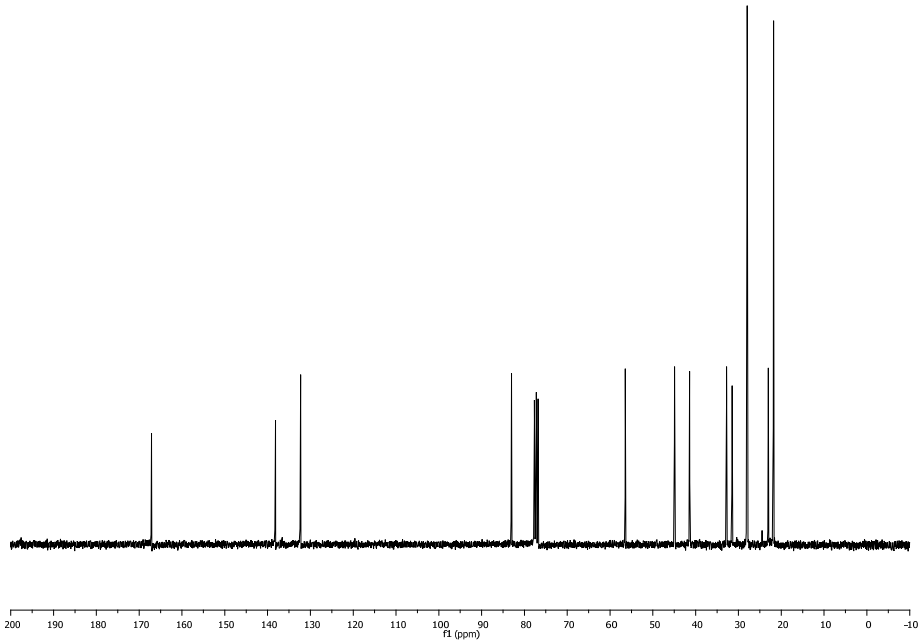
f1 (ppm)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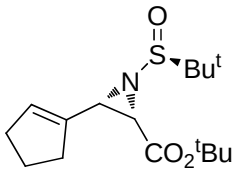
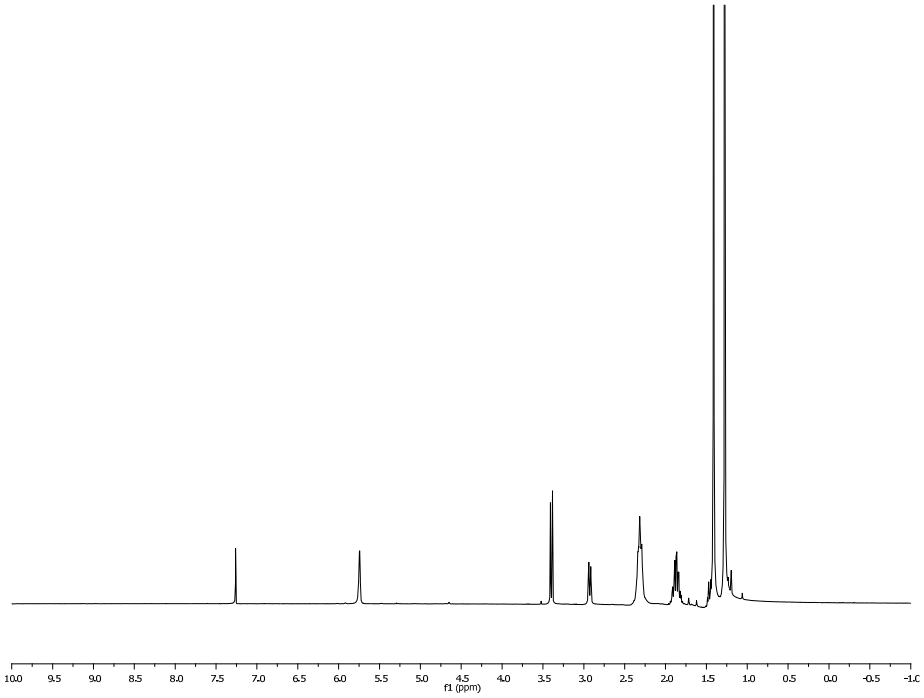
f1 (ppm)


O
S
Bu^t
N
CO2^tBu

3.26l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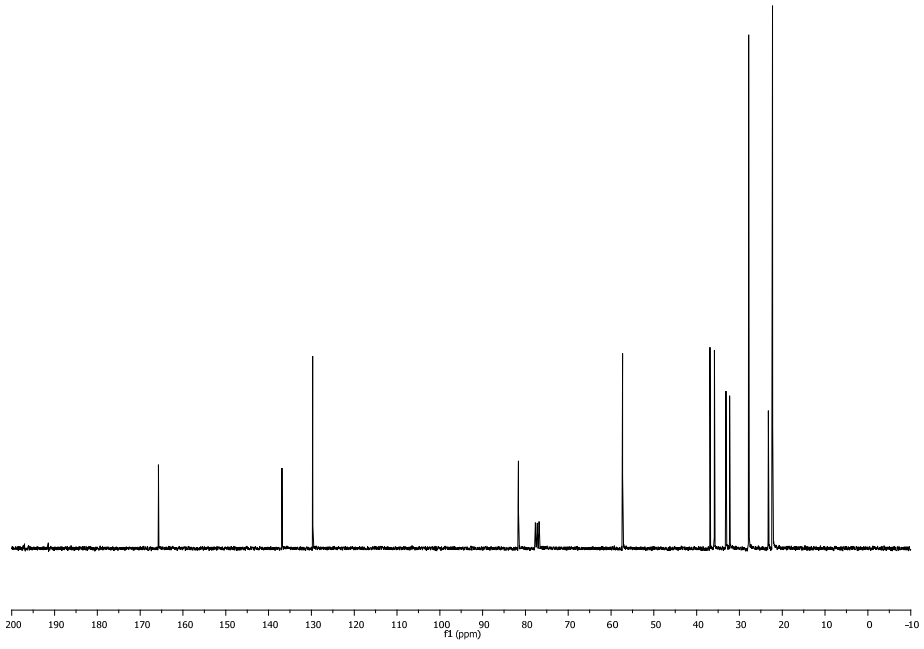
f1 (ppm)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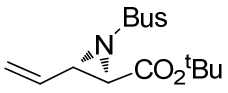
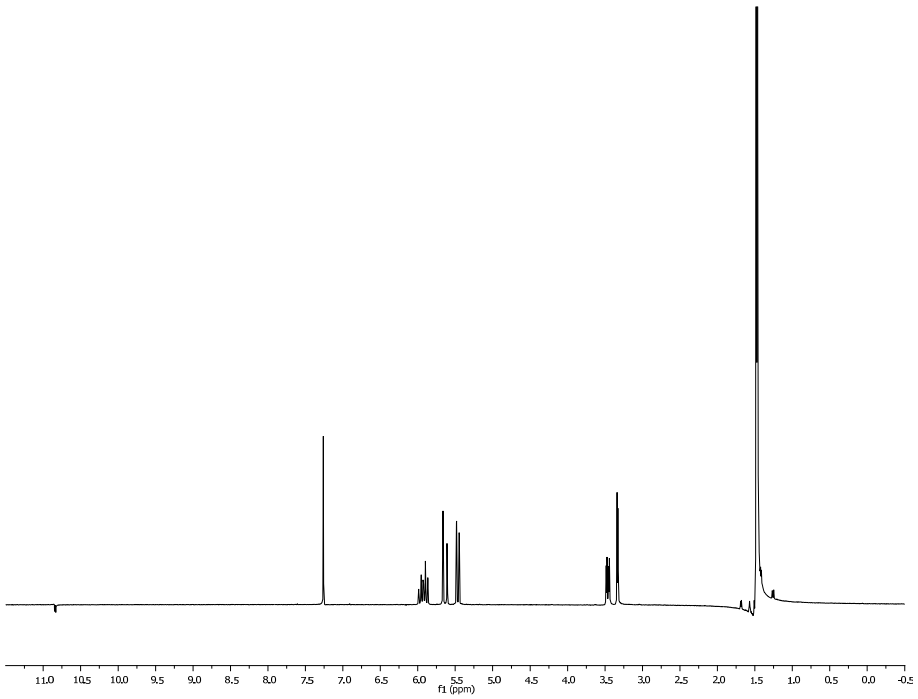
f1 (ppm)


Bus
N
CO2tBu

3.24a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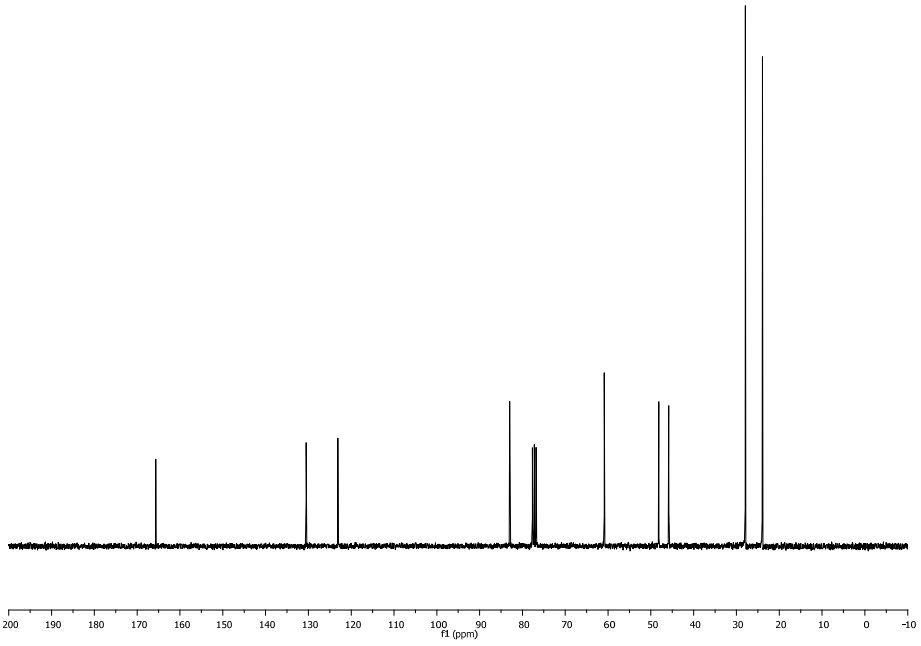
f1 (ppm)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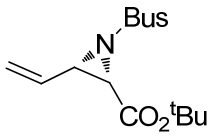
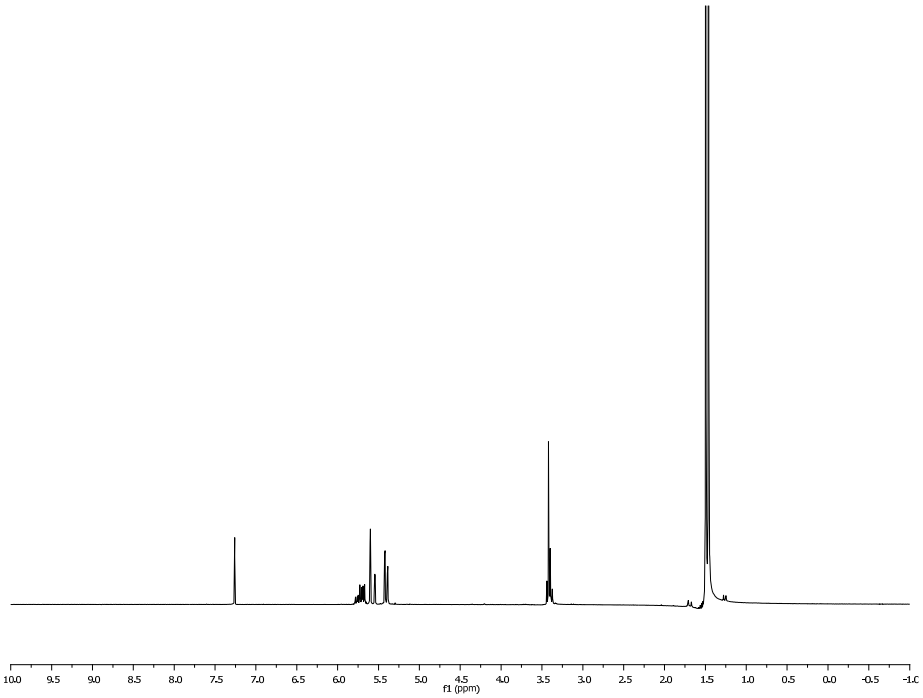
f1 (ppm)


Bus
N
CO2tBu

3.24b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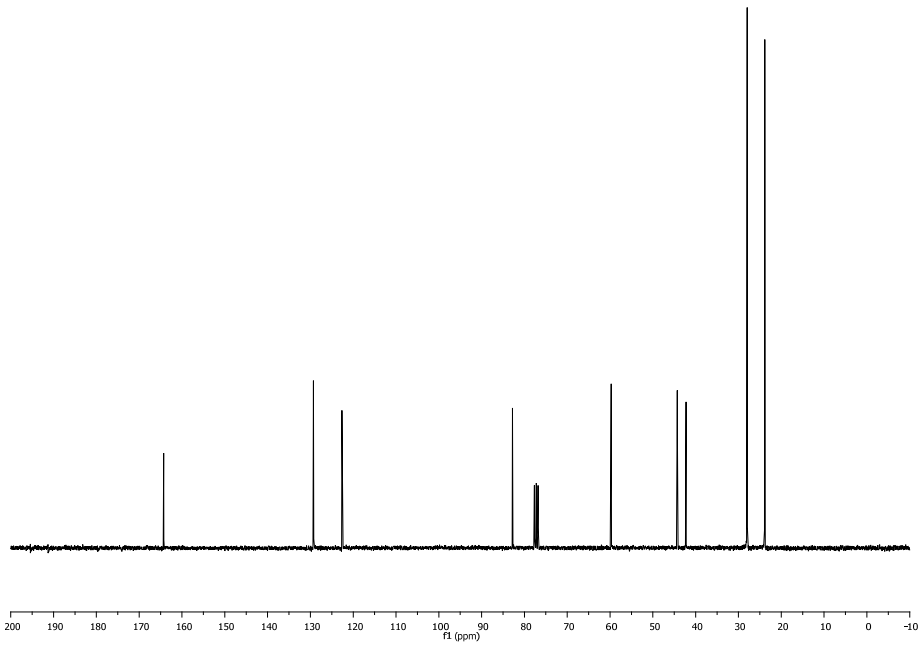
f1 (ppm)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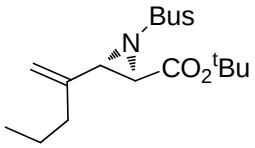
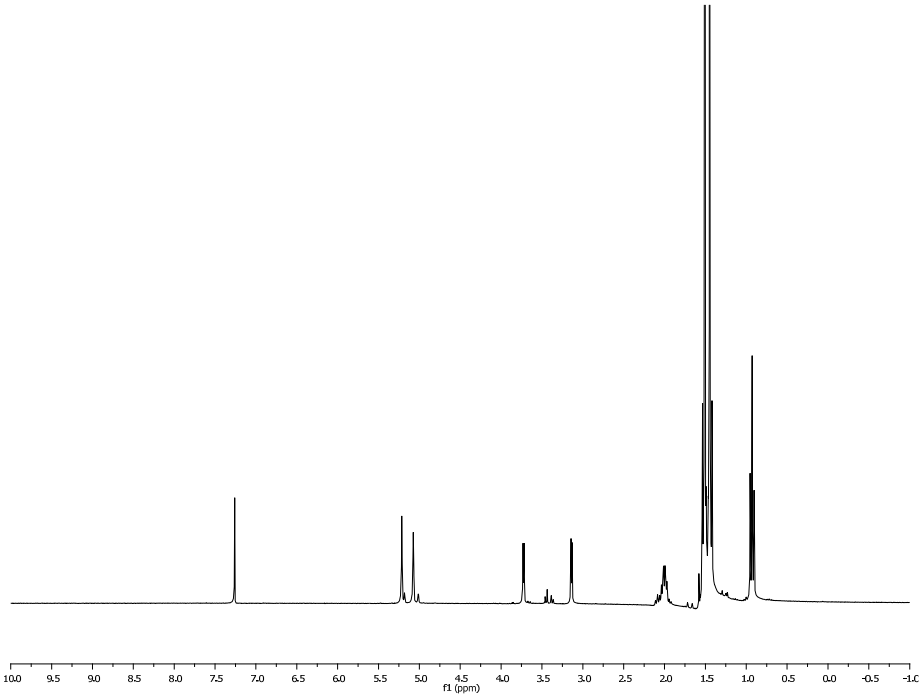
f1 (ppm)


Bus
N
CO2tBu

3.24c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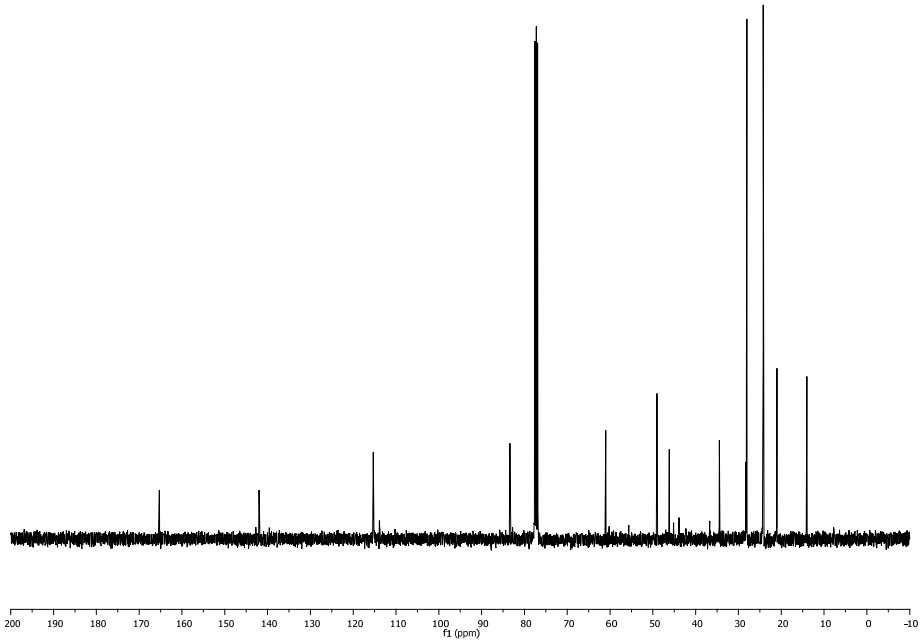
f1 (ppm)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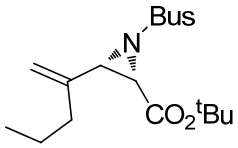
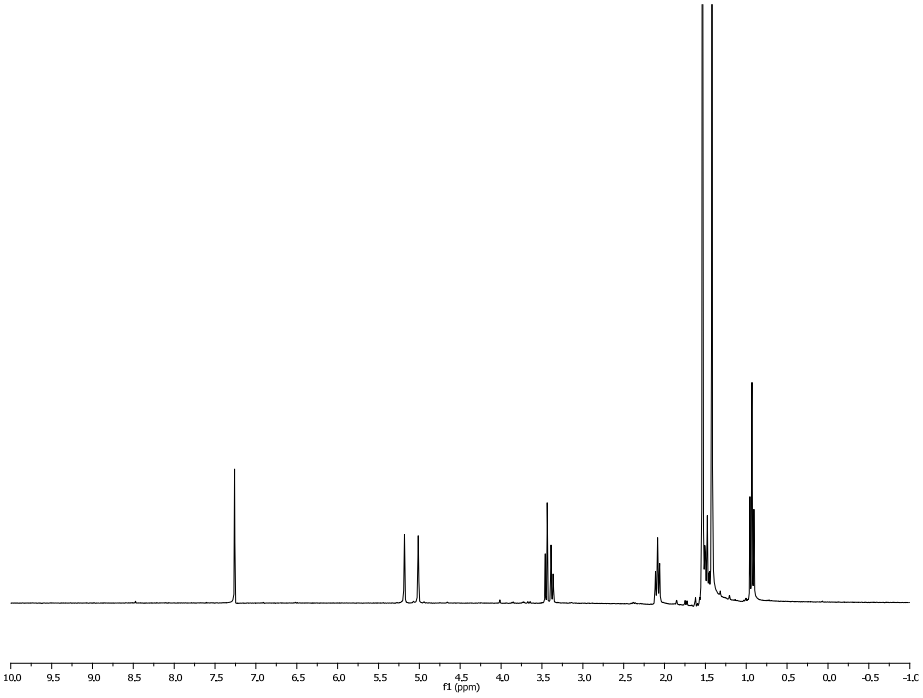
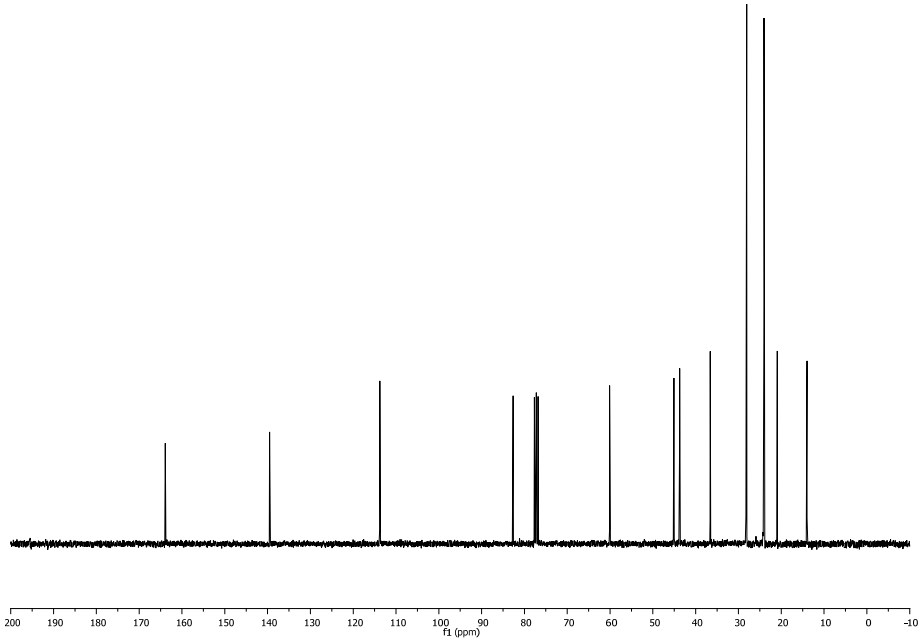
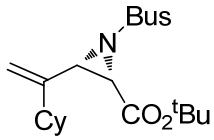


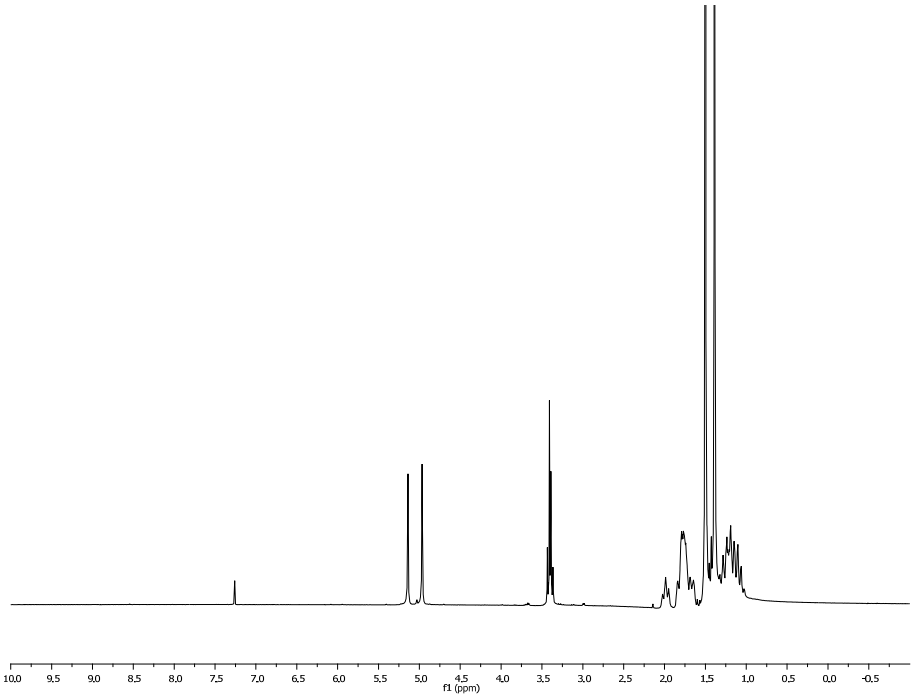
3.24d






Bus
N
Cy
CO2tBu

3.24f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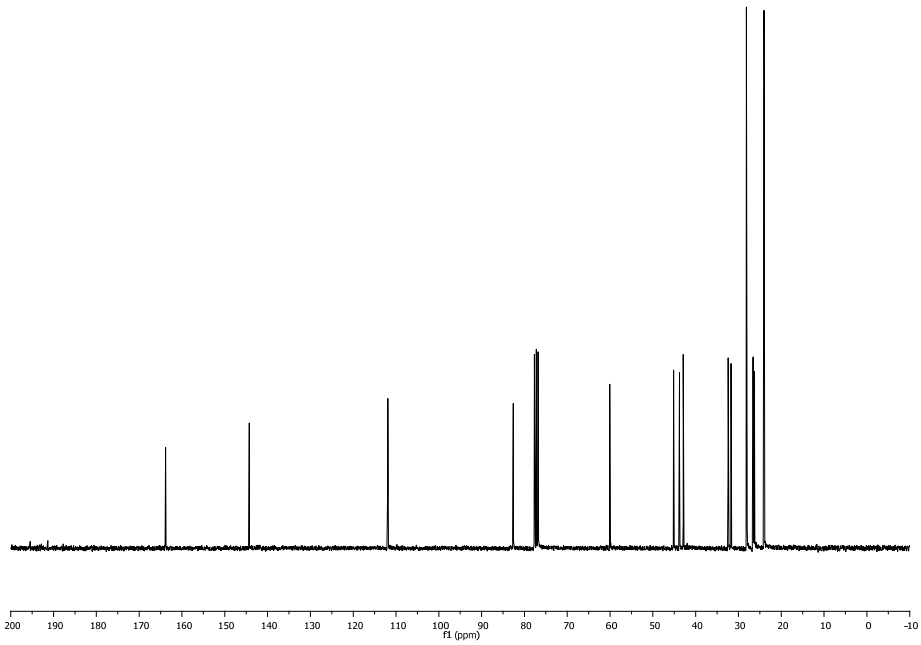
f1 (ppm)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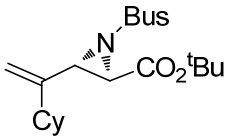
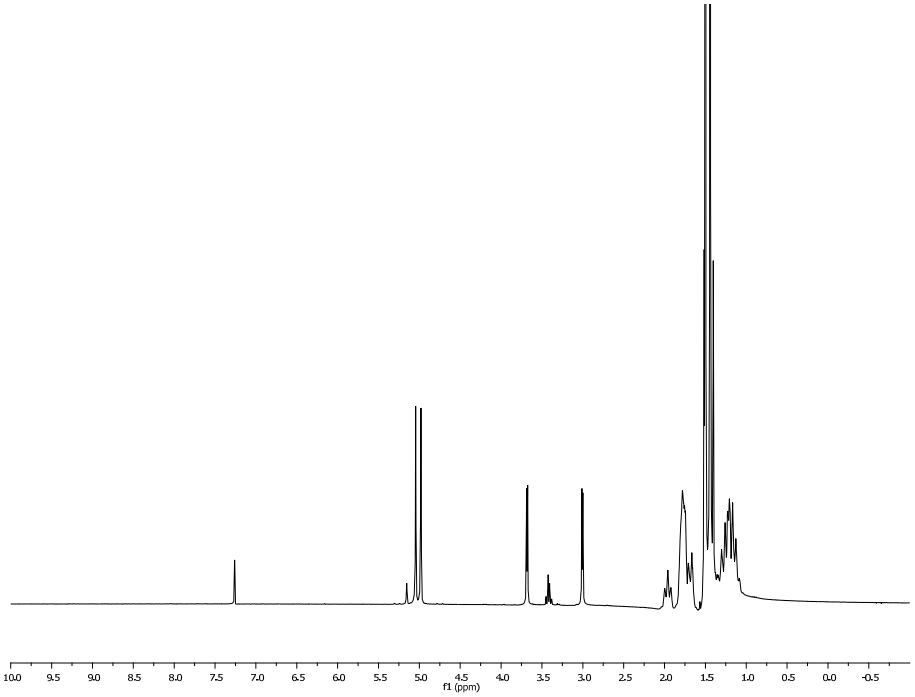

Bus
N
CO2tBu
Cy

3.24g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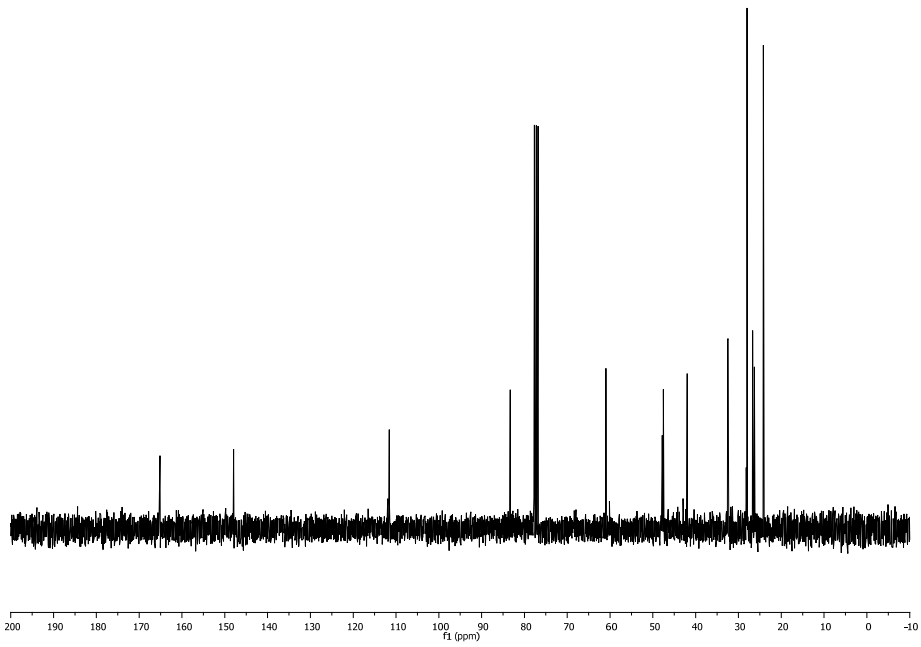
f1 (ppm)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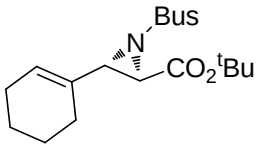
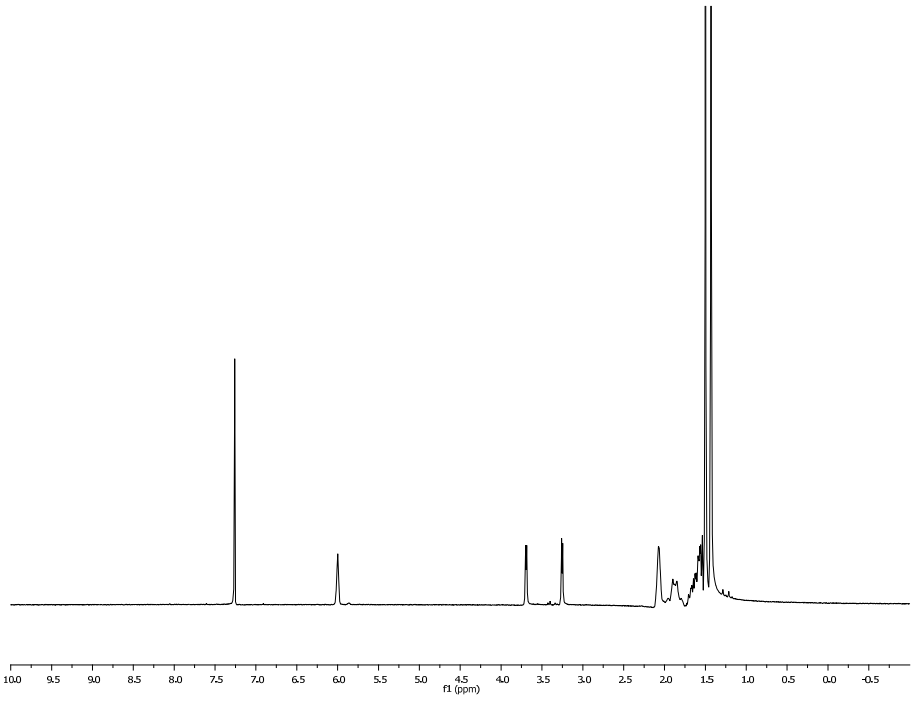

Bus
N
CO2tBu

3.24i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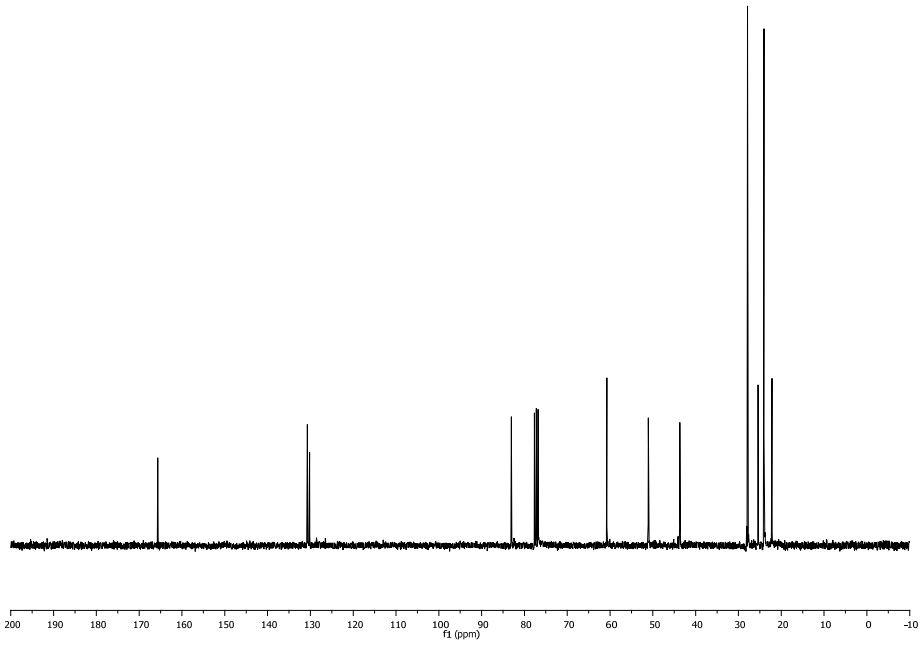
f1 (ppm)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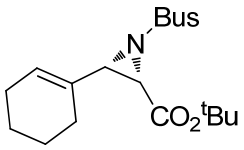
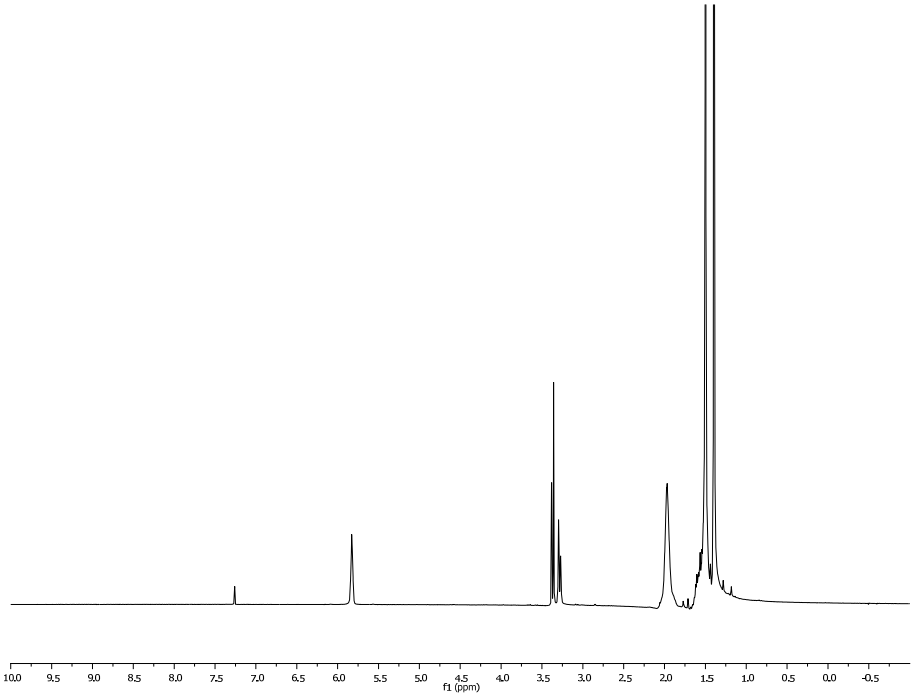
f1 (ppm)


Bus
N
CO2tBu

3.24i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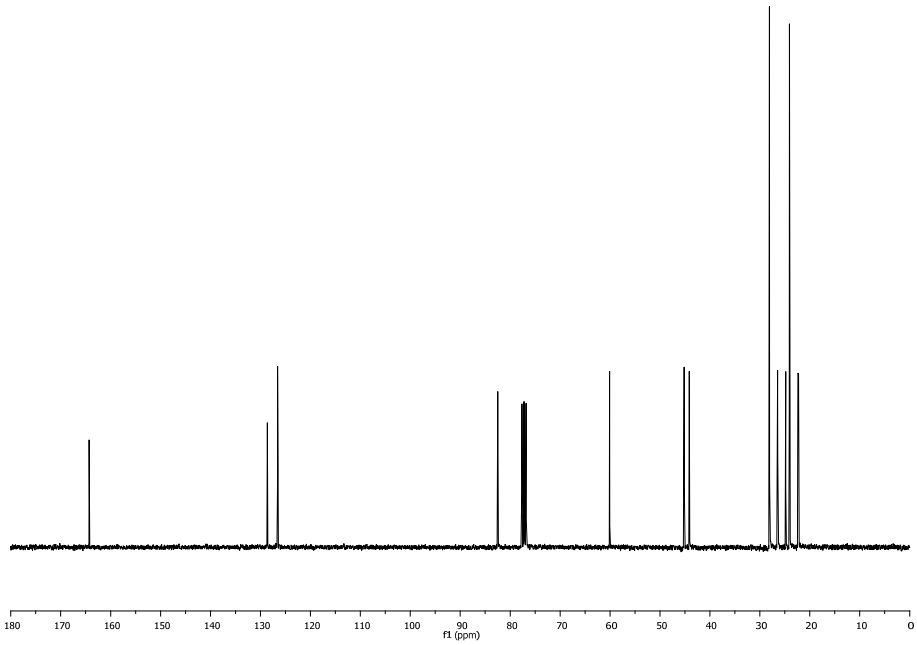
f1 (ppm)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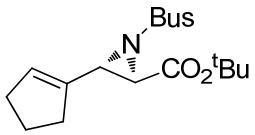
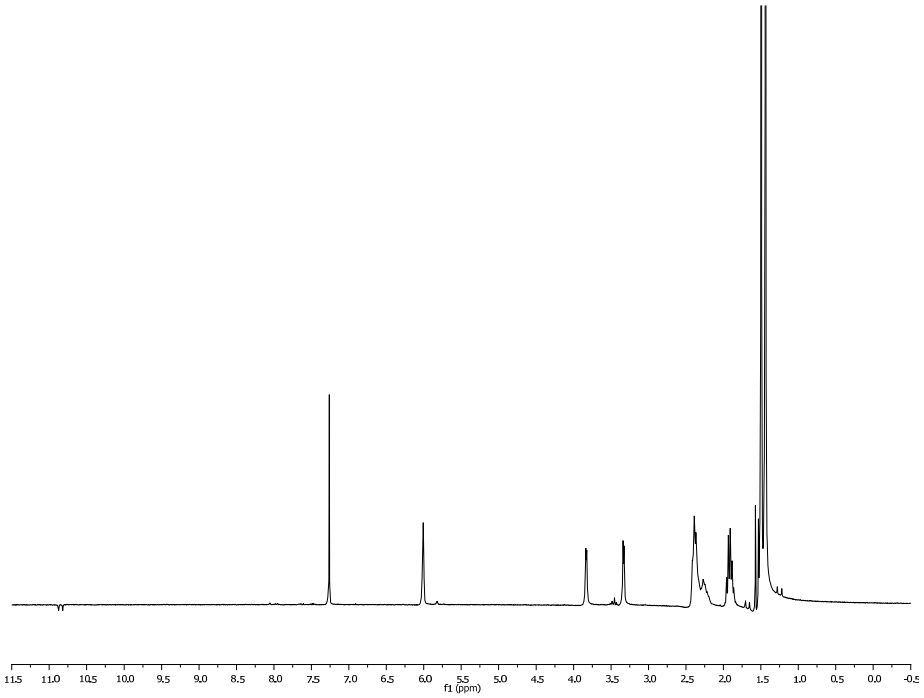
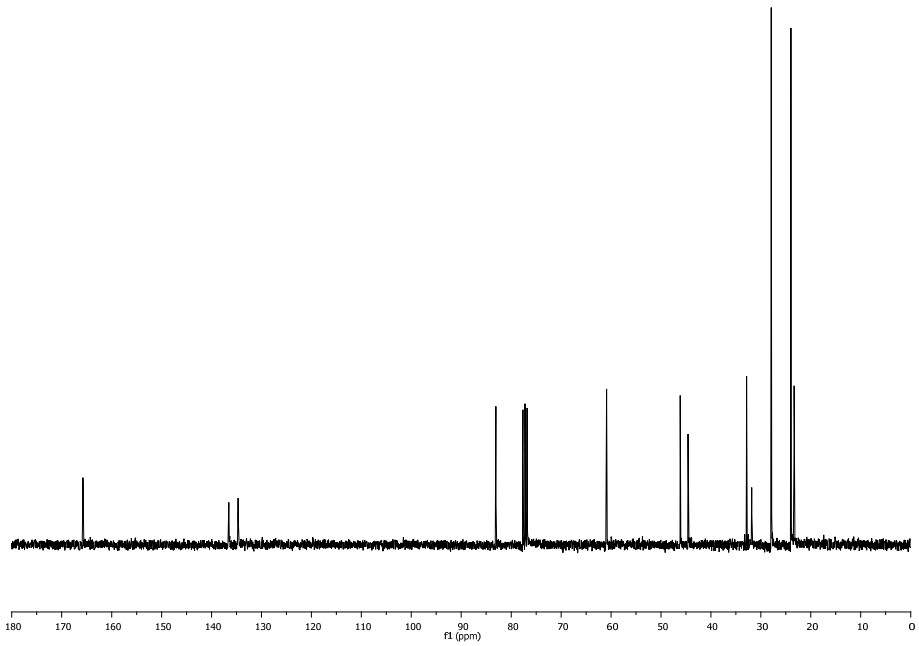
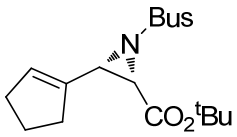
f1 (ppm)



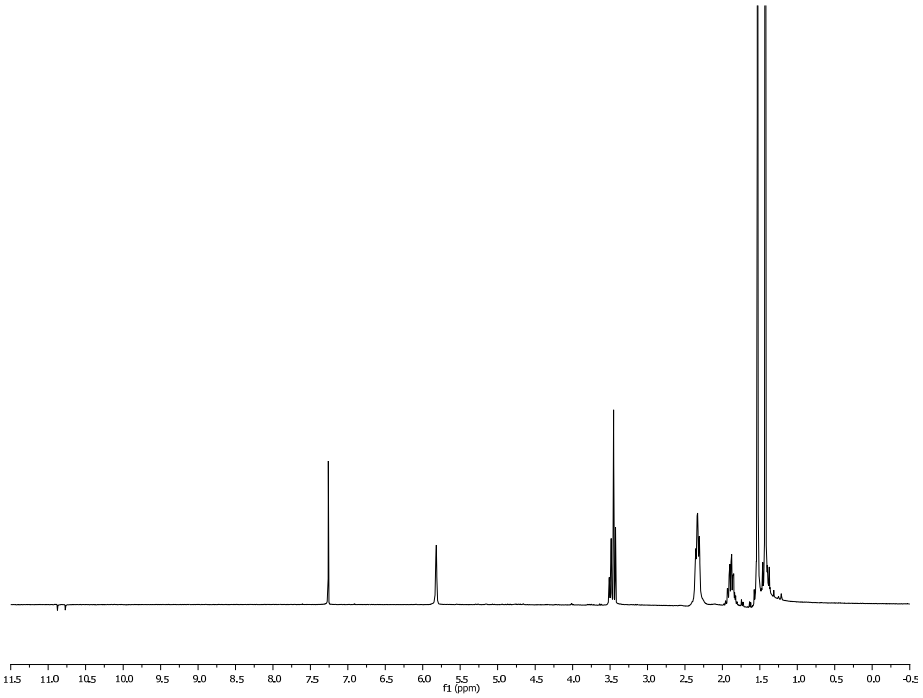
3.24k

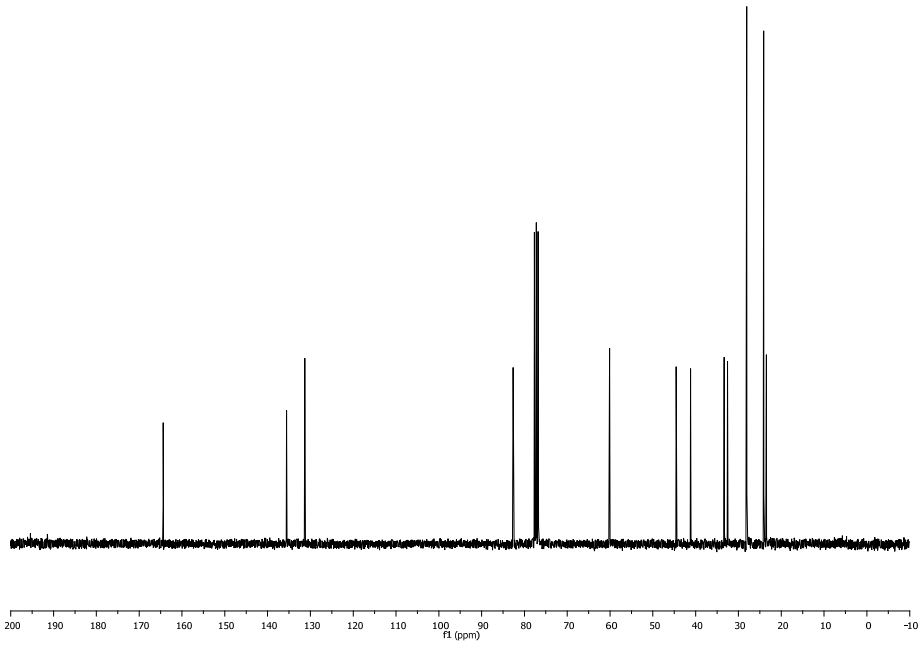


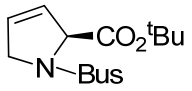




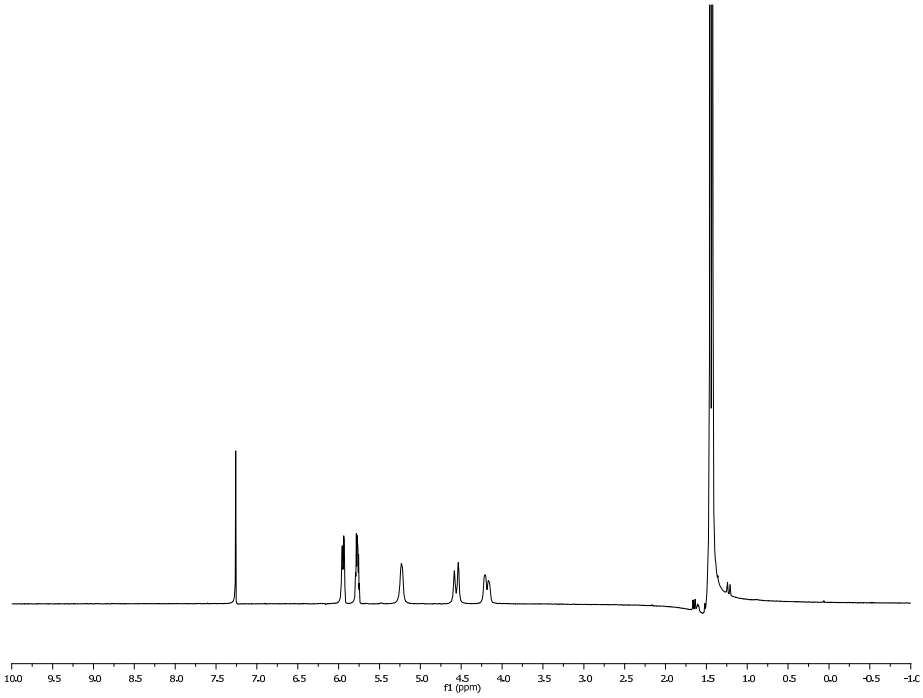
3.24l

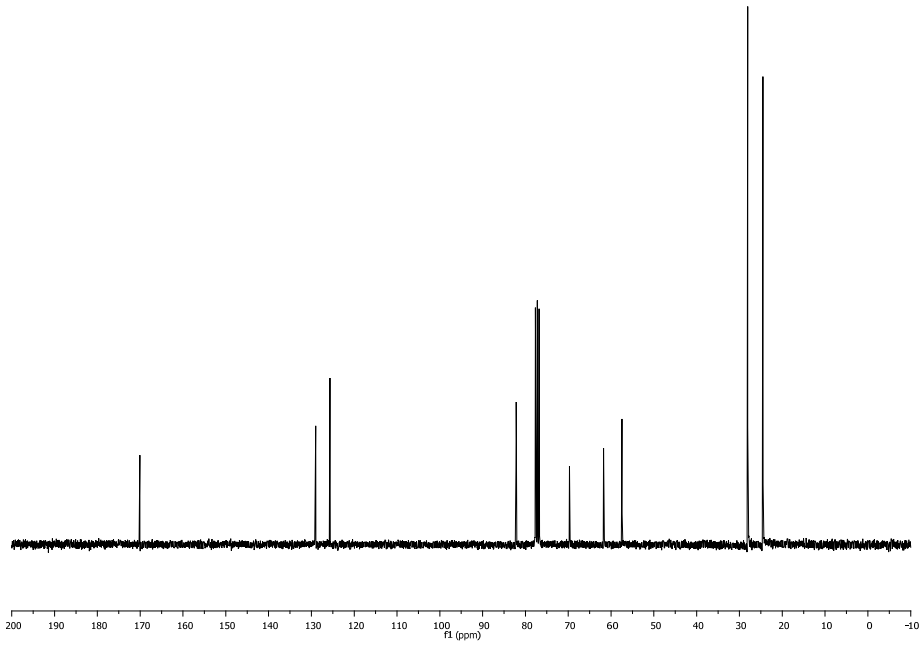


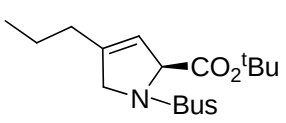


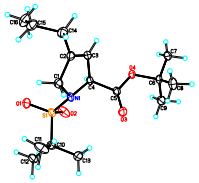


3.25b

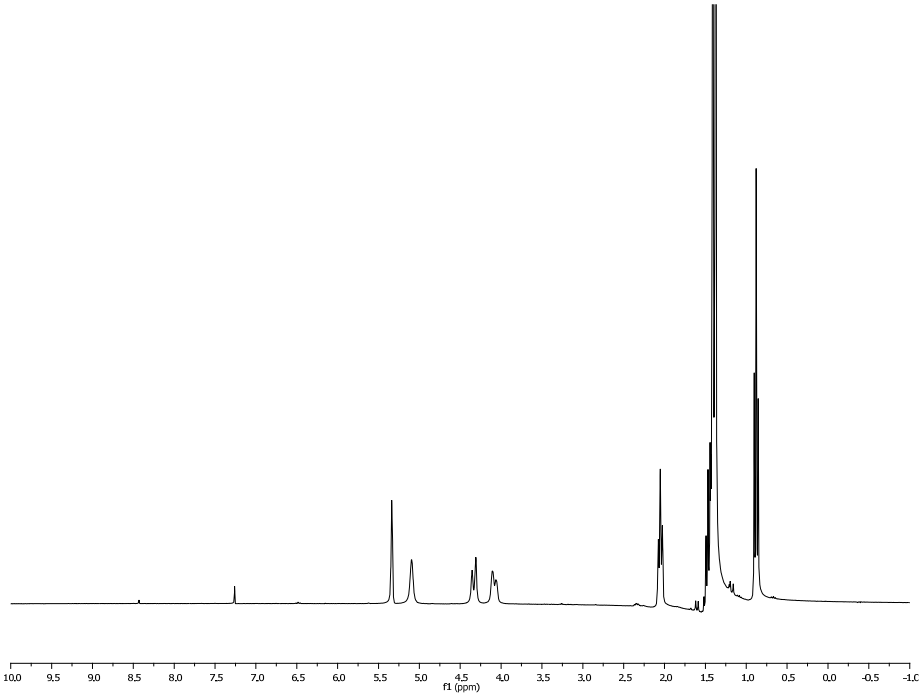


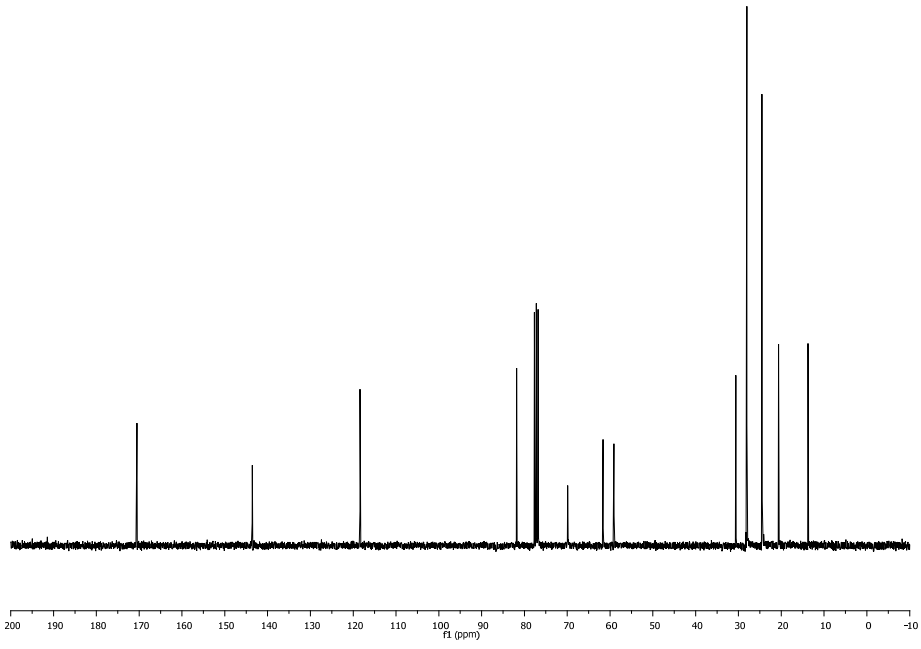


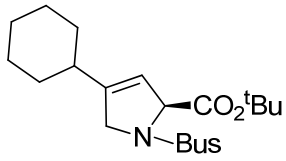

CO2tBu
N
Bus



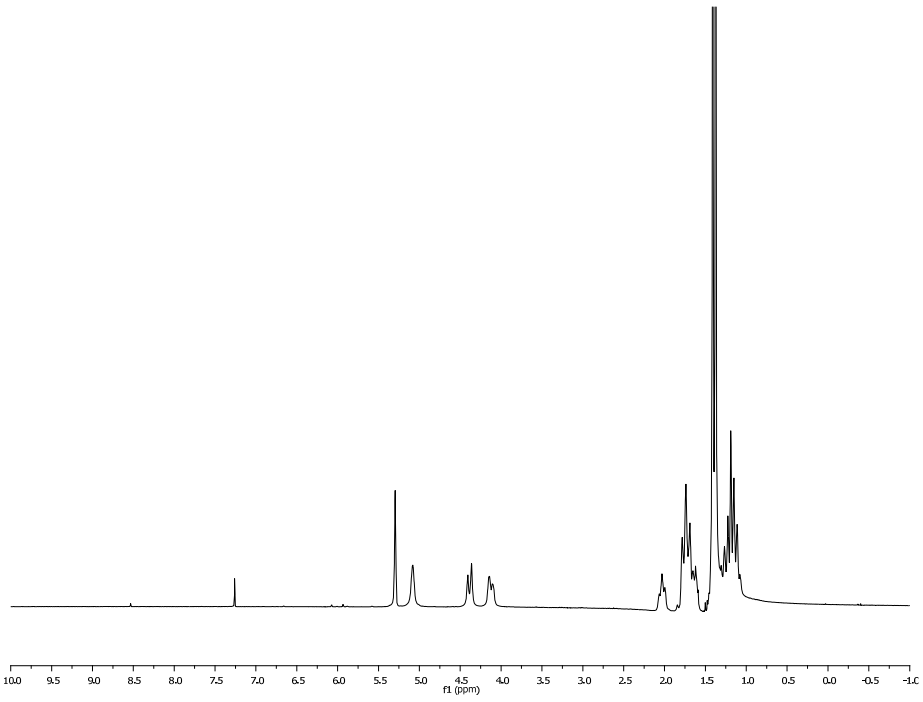
3.25d

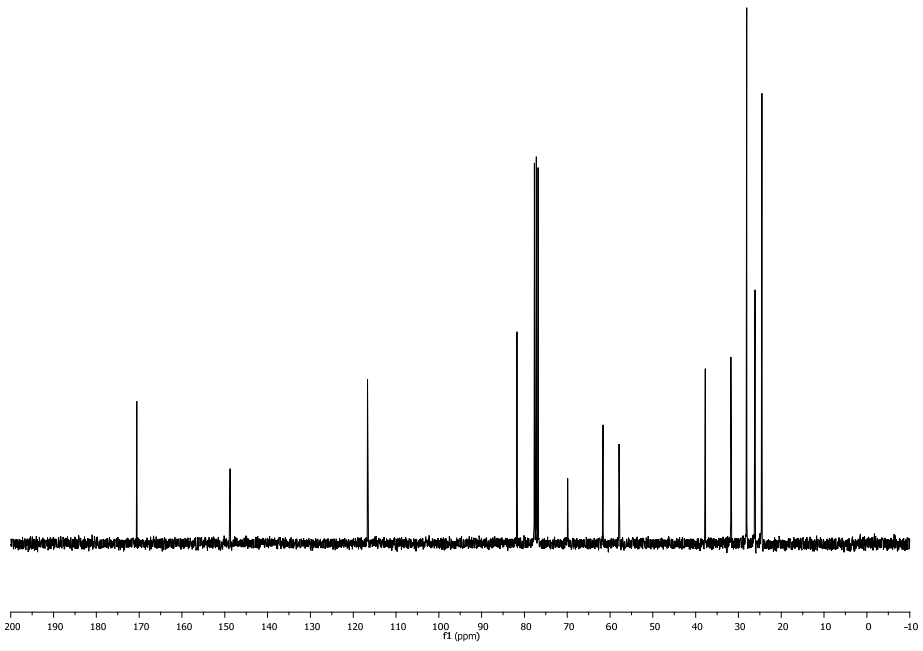

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)


CO2tBu
N
Bus

3.25e


10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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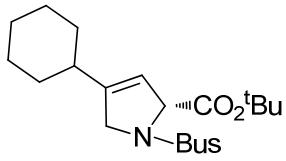
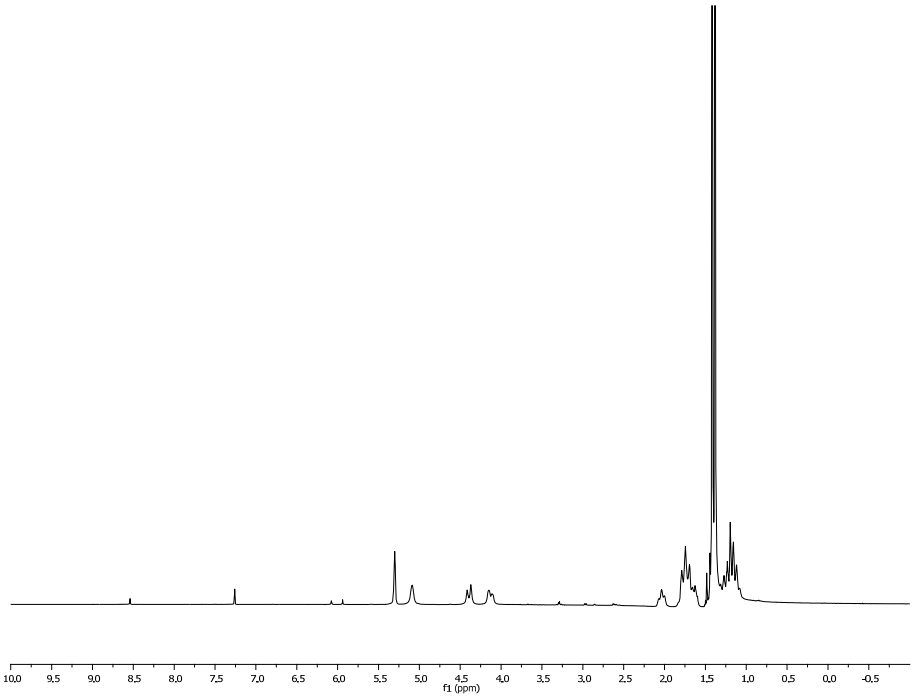
f1 (ppm)


CO2tBu
N
Bus

3.25g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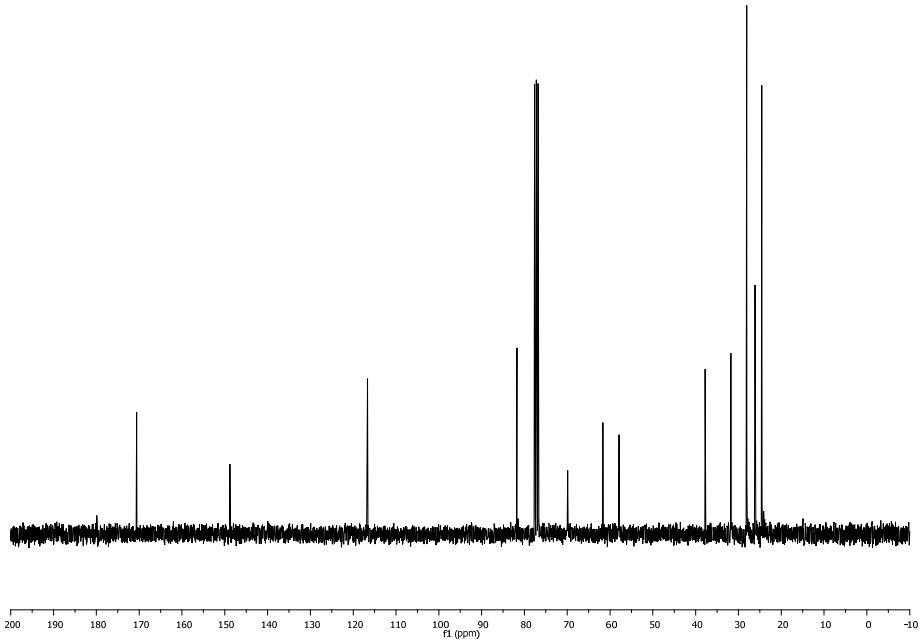
f1 (ppm)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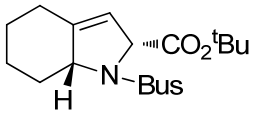
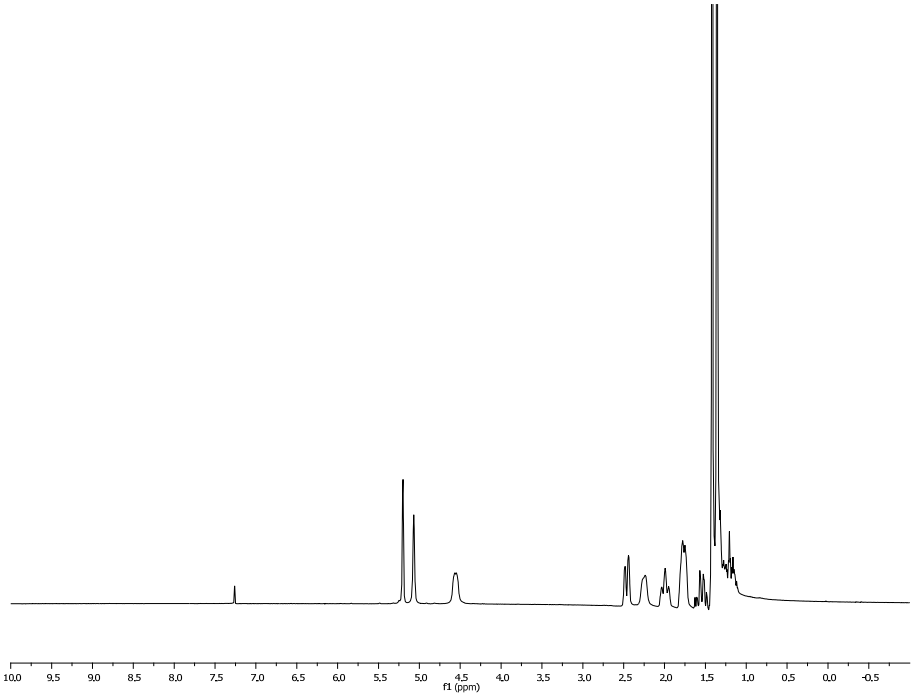
f1 (ppm)


CO2tBu
N
Bus
H

3.25i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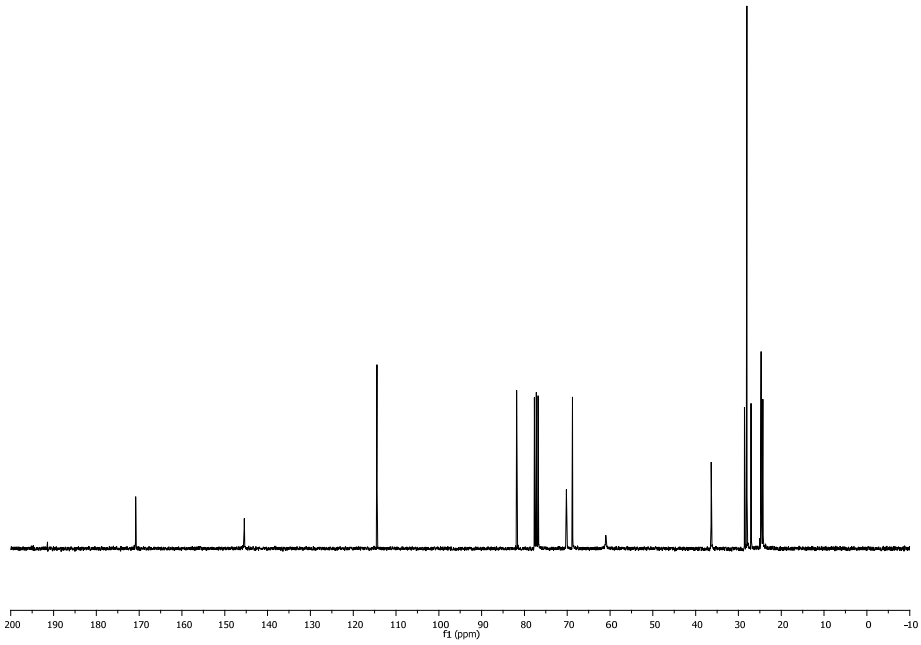
f1 (ppm)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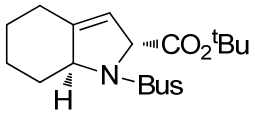
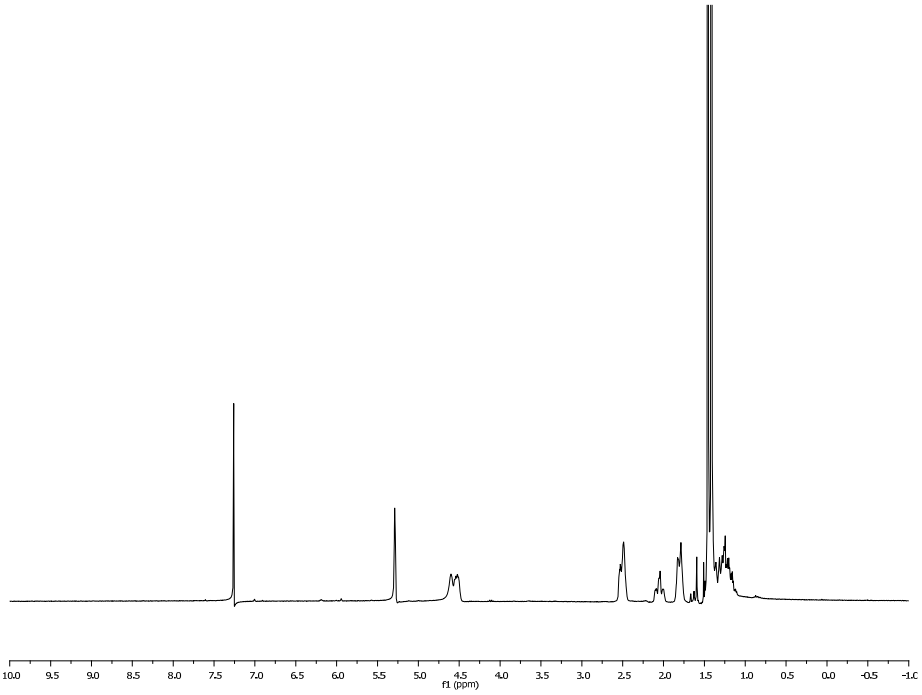
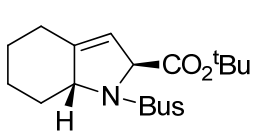
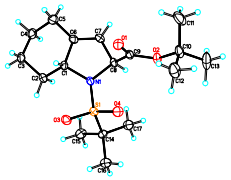
f1 (ppm)


CO2tBu
N
Bus
H

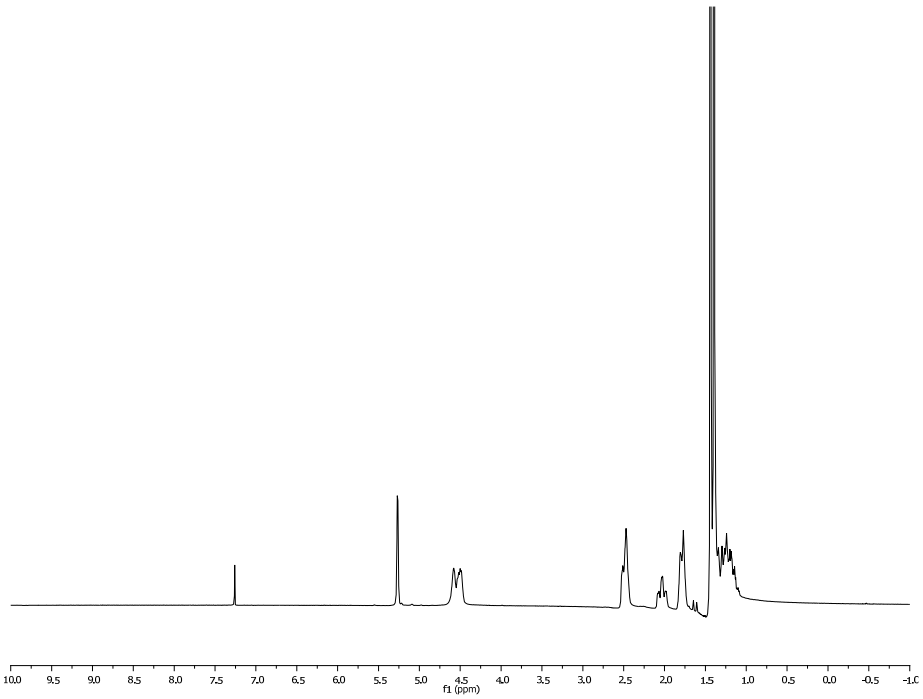
3.25j

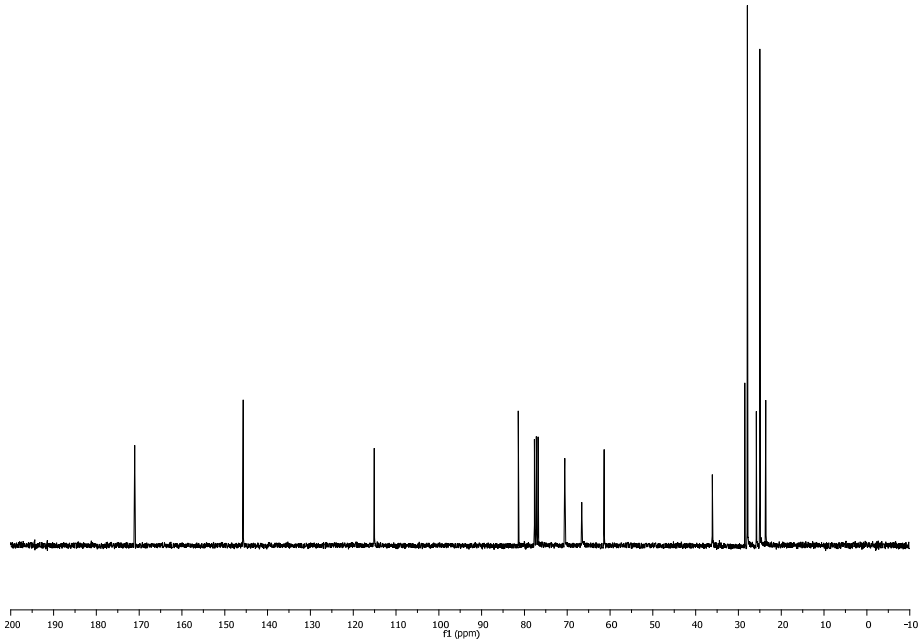

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


CO2tBu
N
Bus
H



3.25j


10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5 -1.0
f1 (ppm)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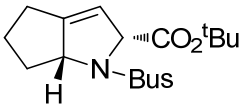
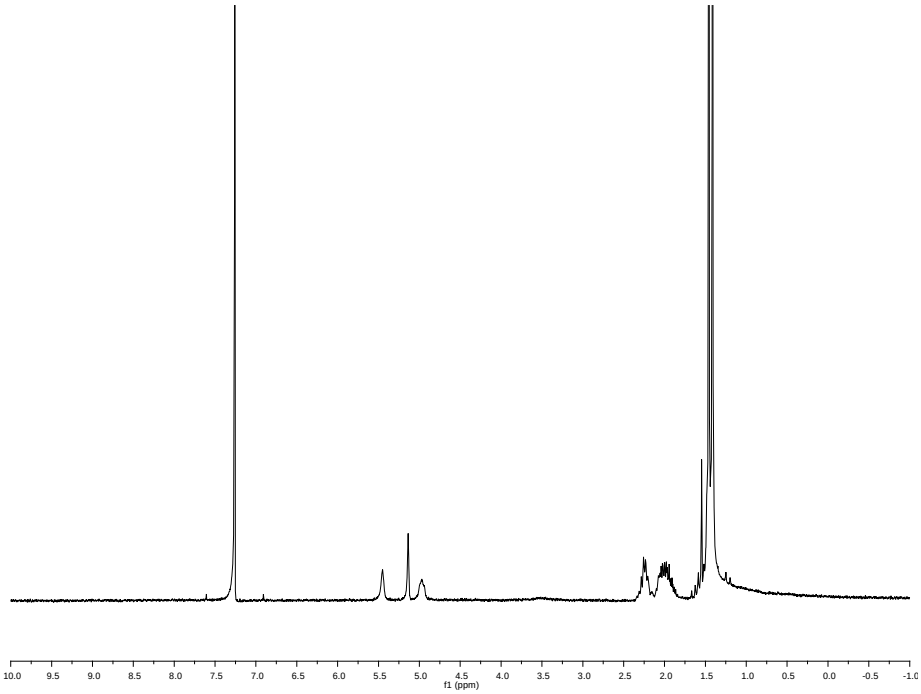
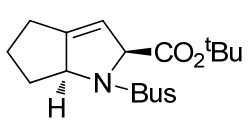
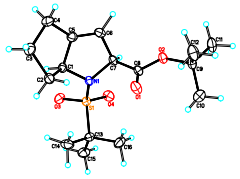
f1 (ppm)


CO2tBu
N
Bus
H

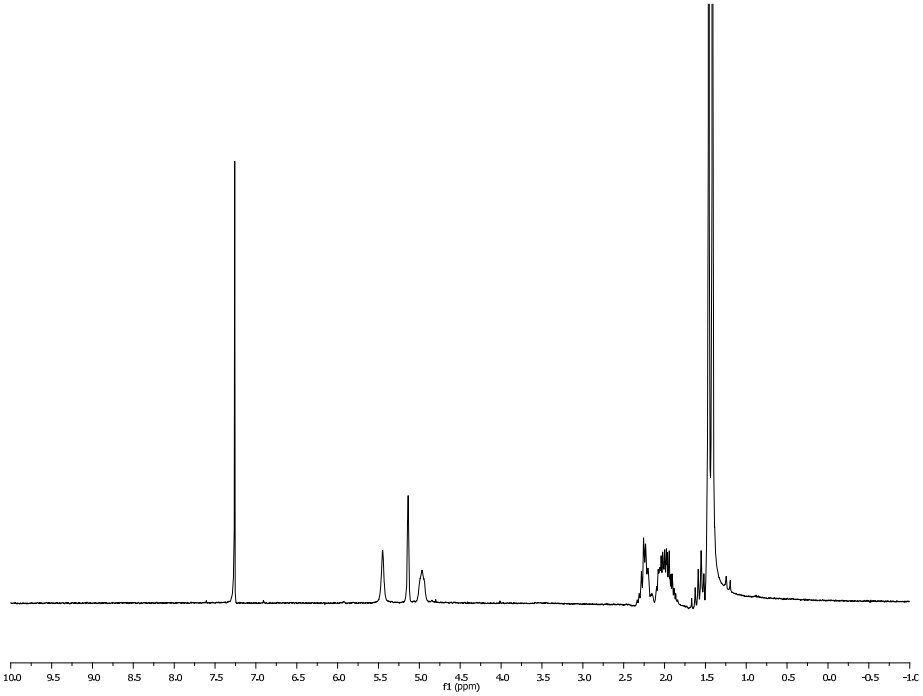
3.25k

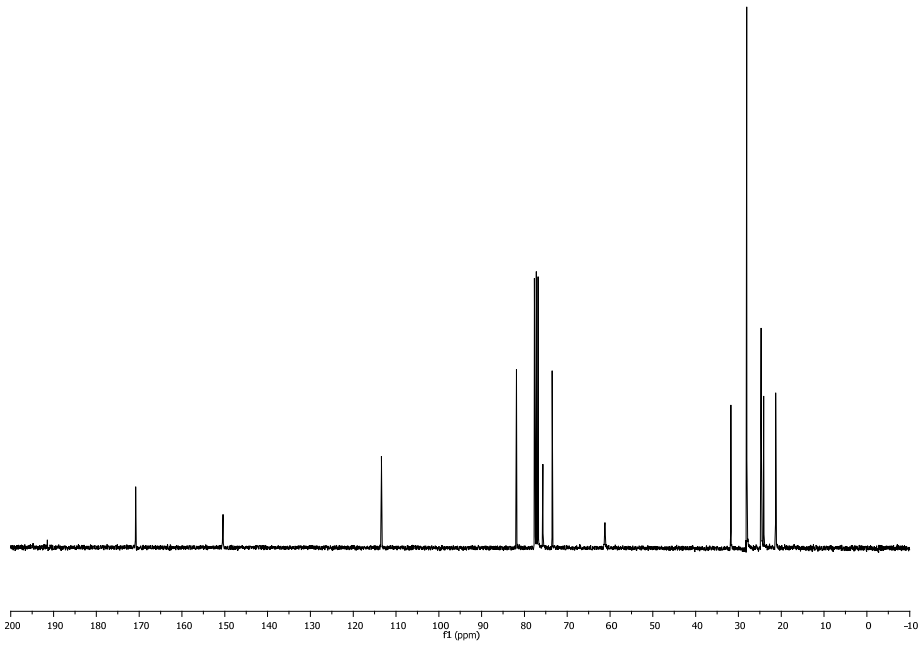

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)


CO2tBu
N
Bus
H



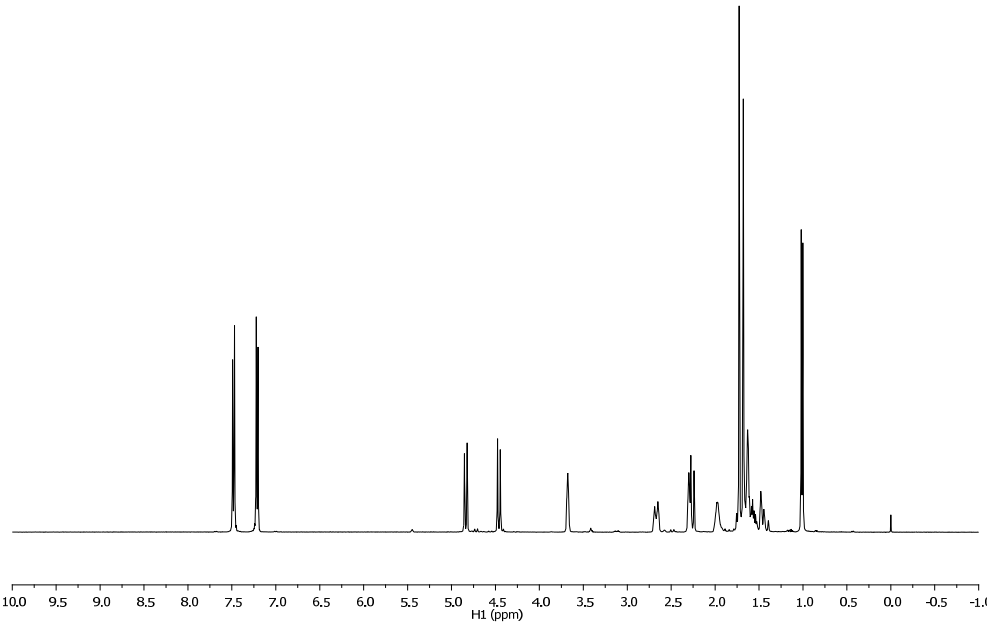
3.24l


10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)


OTf
S
Cl

3.29a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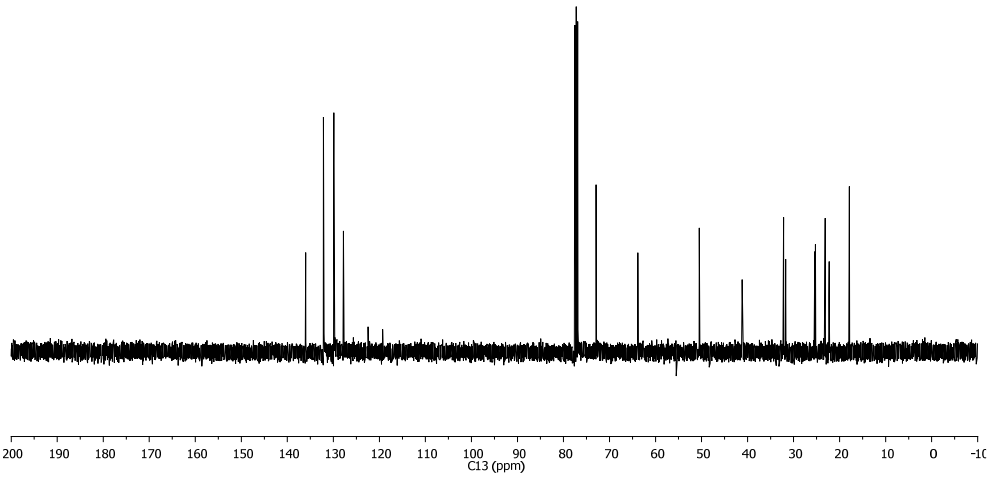
H1 (ppm)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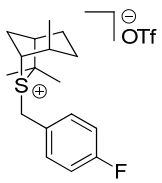
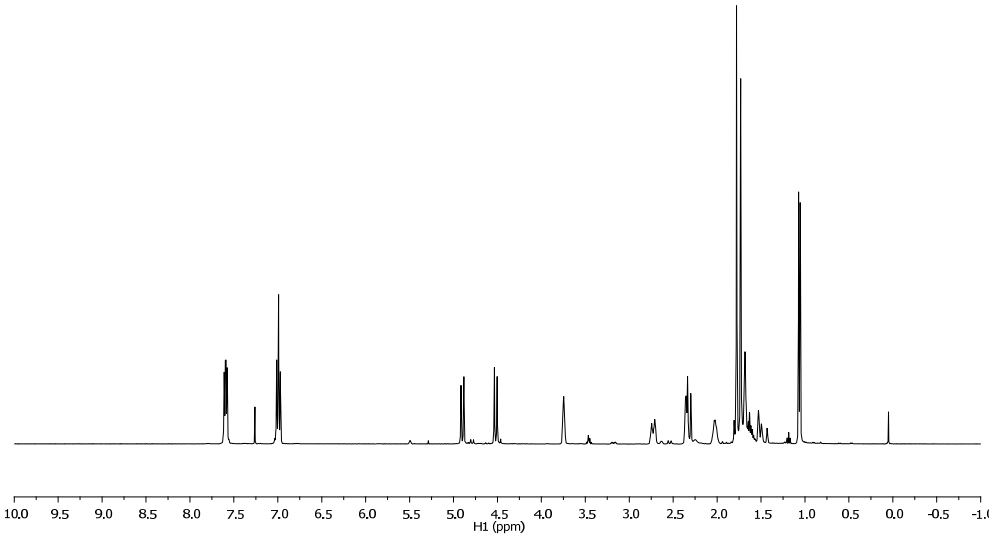
C13 (ppm)


OTf
S
F

3.29b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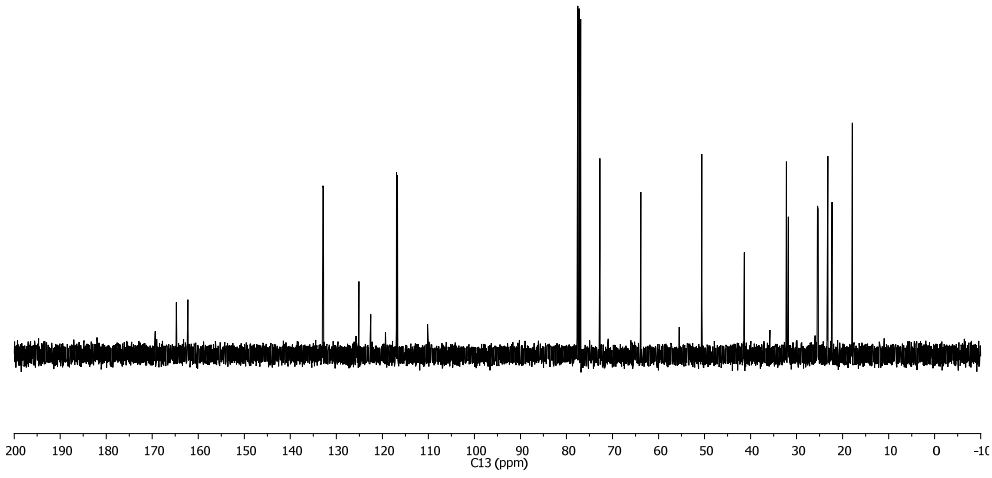
H1 (ppm)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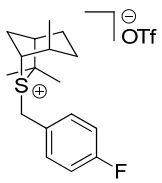
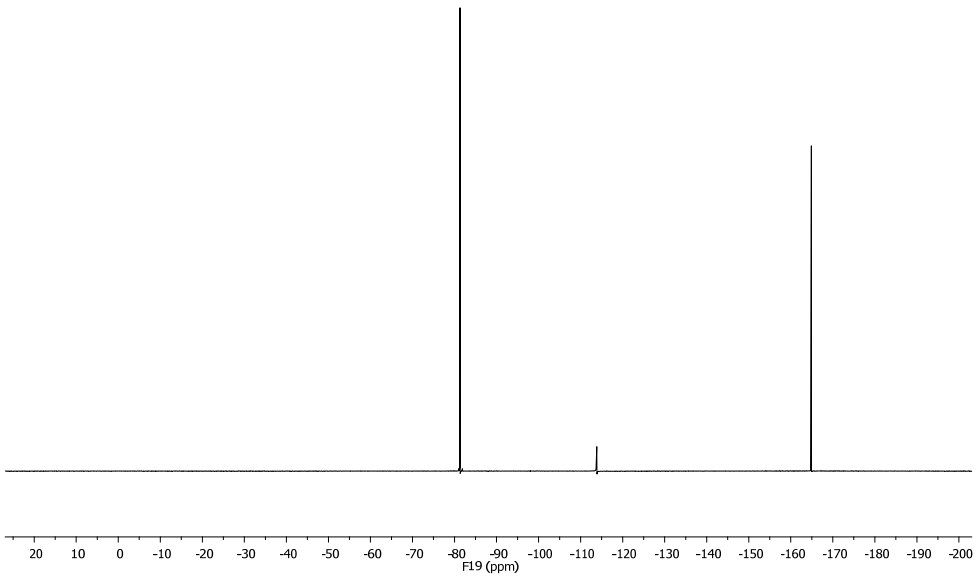
C13 (ppm)


OTf
S
F

3.29b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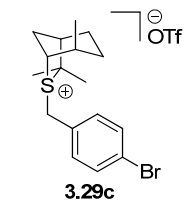
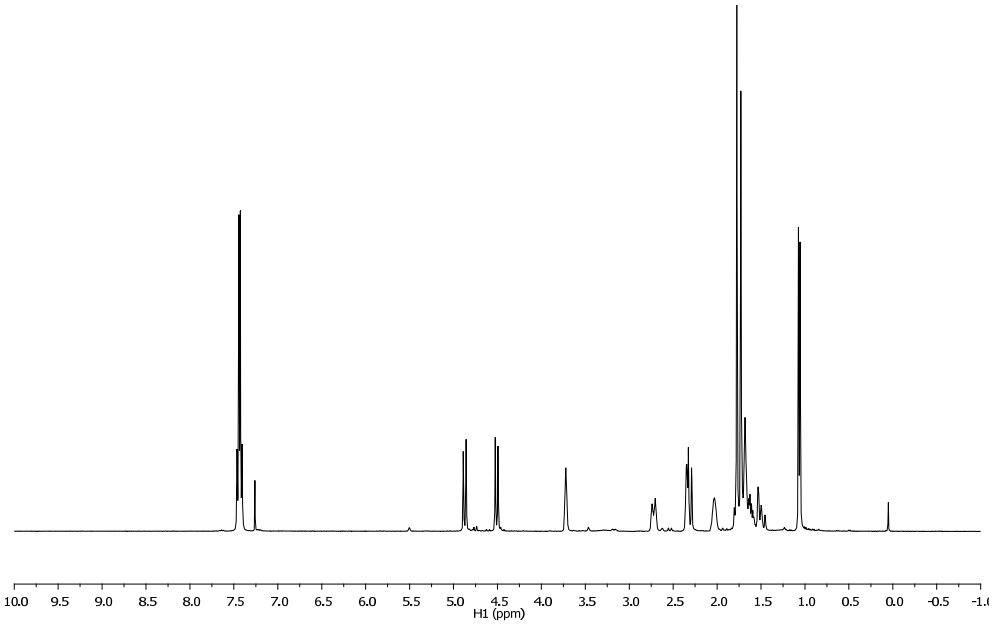
F19 (ppm)


OTf
S
Br

3.29c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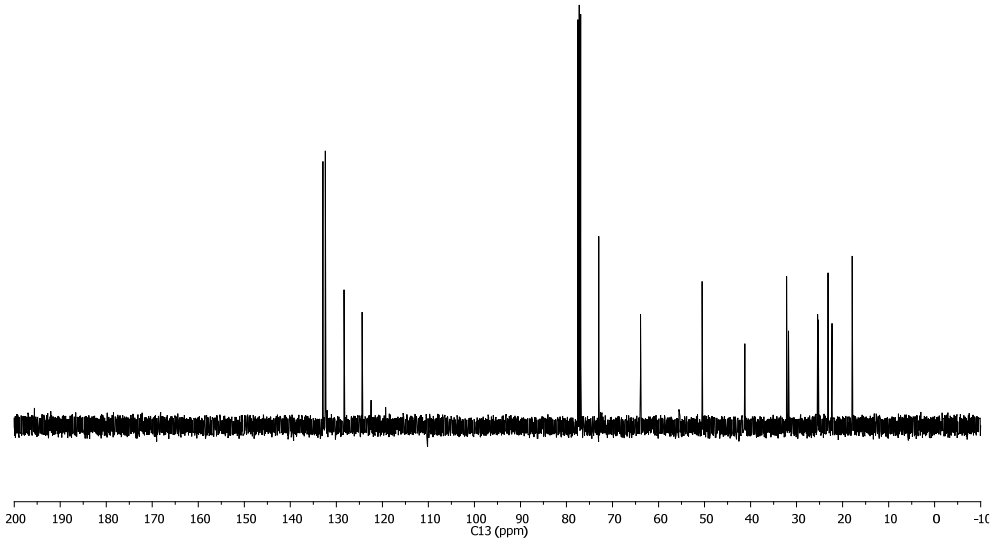
H1 (ppm)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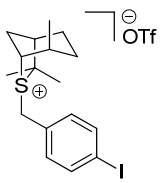
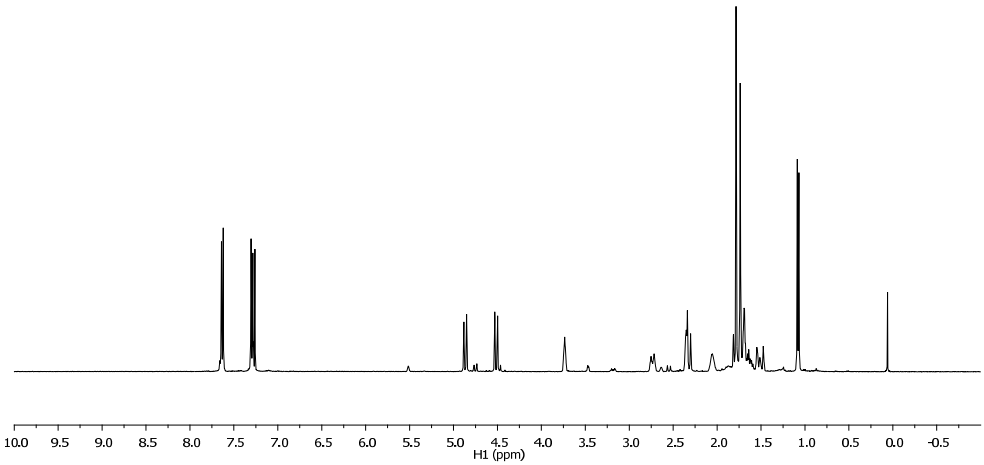
C13 (ppm)


OTf
S
I

3.29d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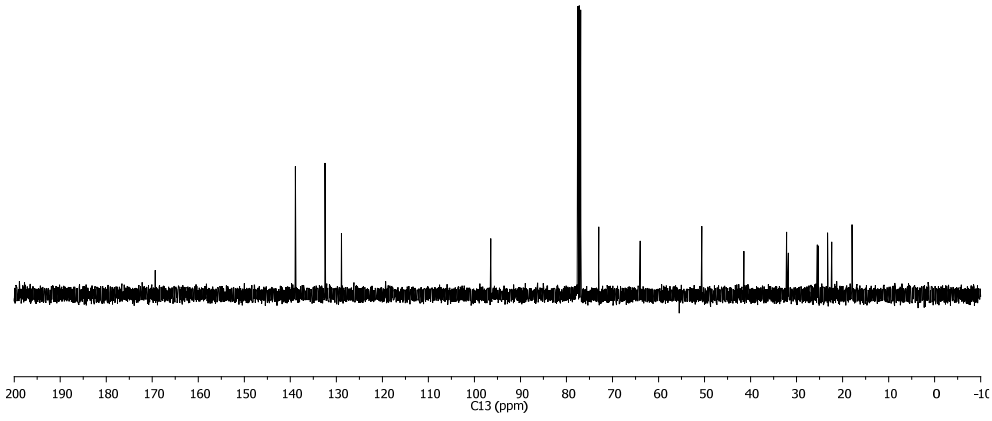
H1 (ppm)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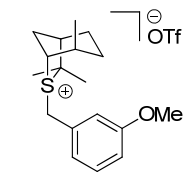
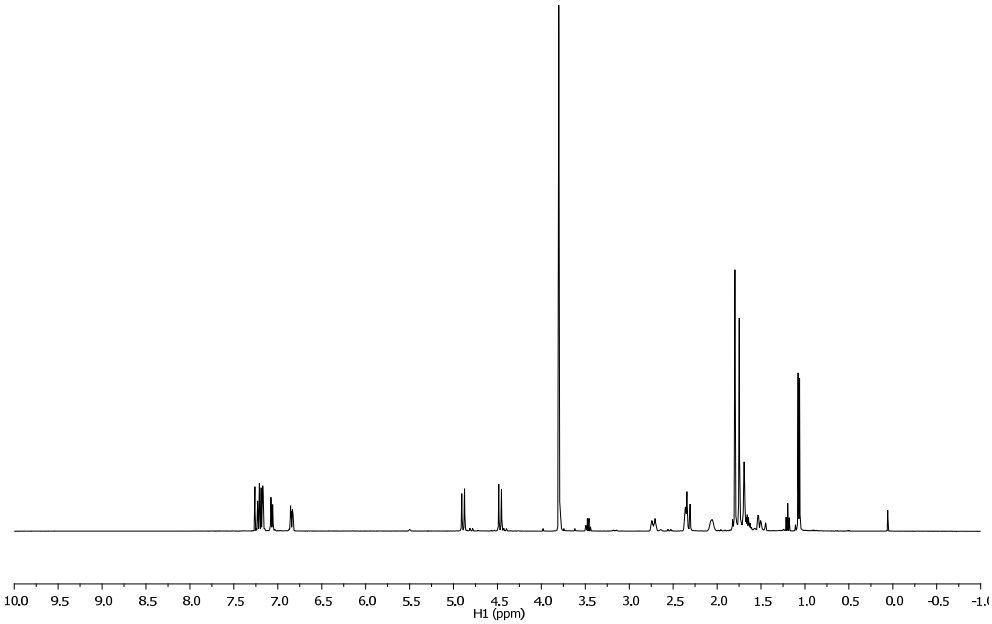
C13 (ppm)


OTf
S
OMe

3.29e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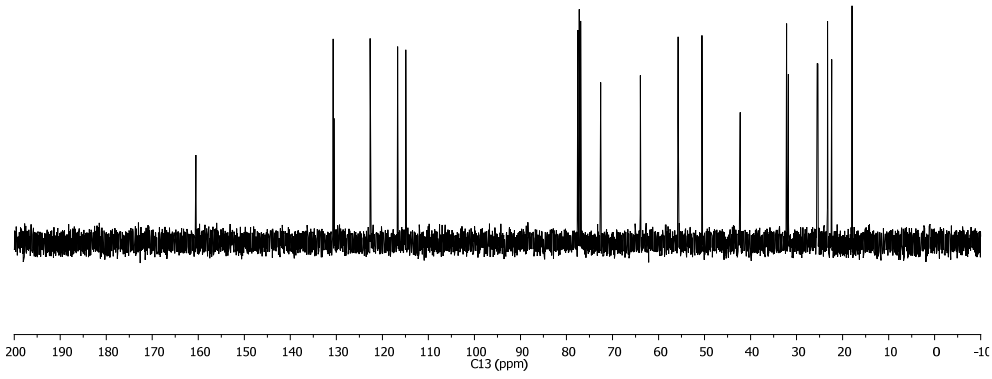
H1 (ppm)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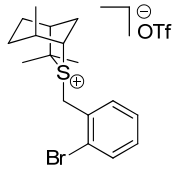
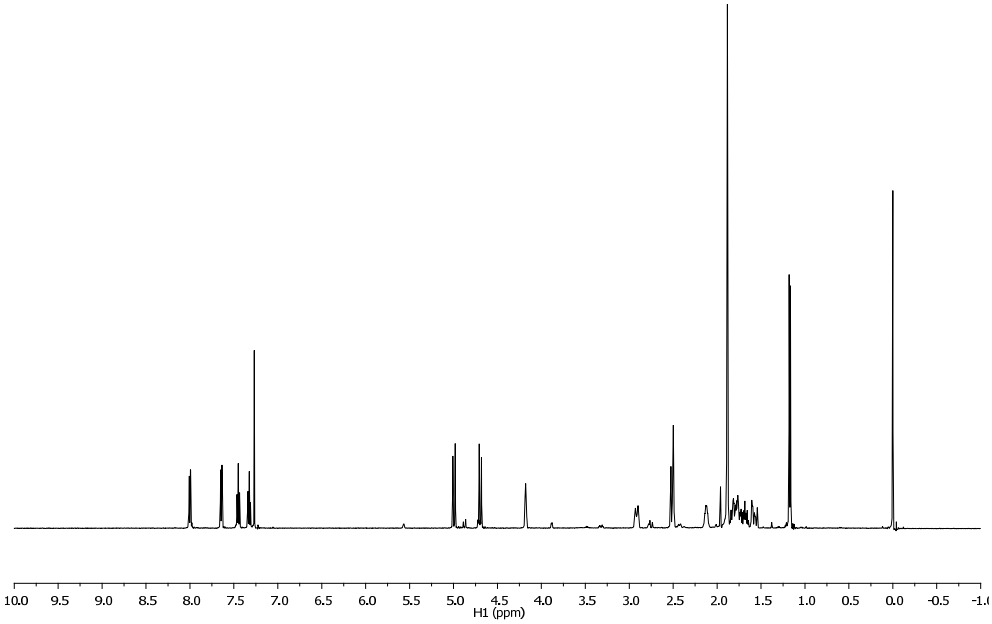
C13 (ppm)


OTf
S
Br

3.29f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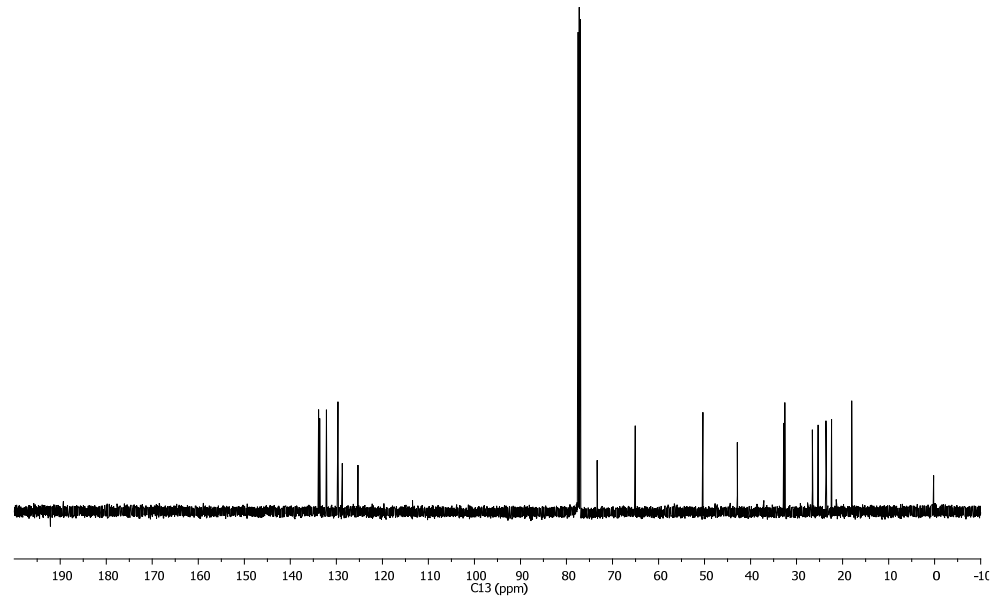
H1 (ppm)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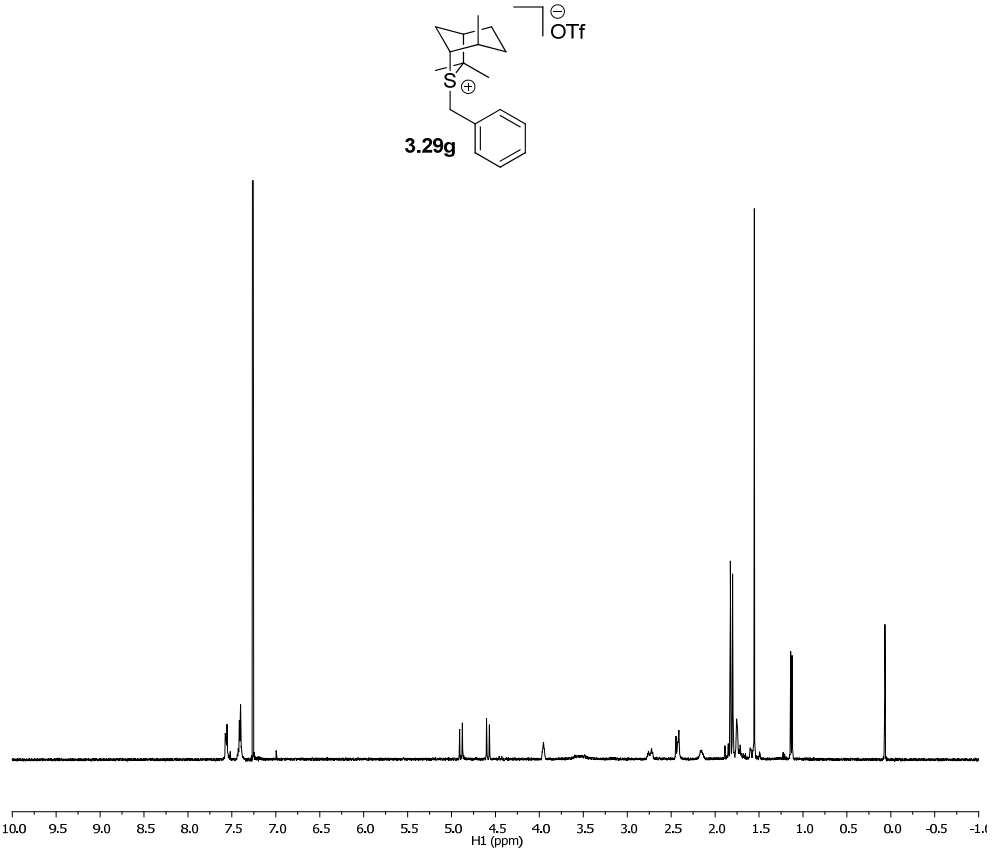
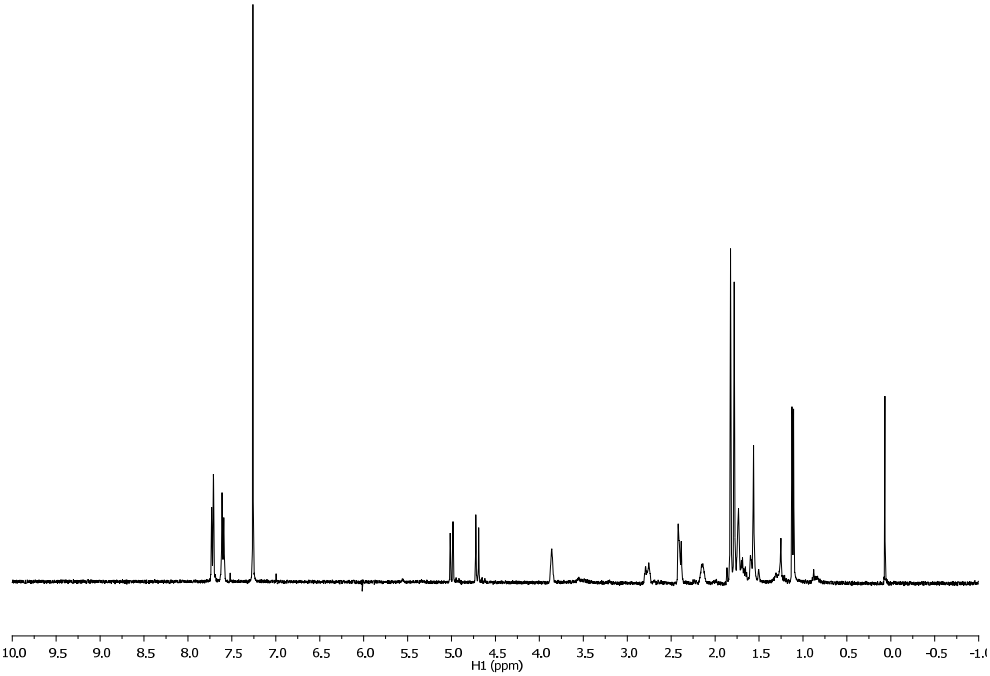
C13 (ppm)


OTf
S
3.29g
10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
H1 (ppm)


OTf
S
CF3

3.29h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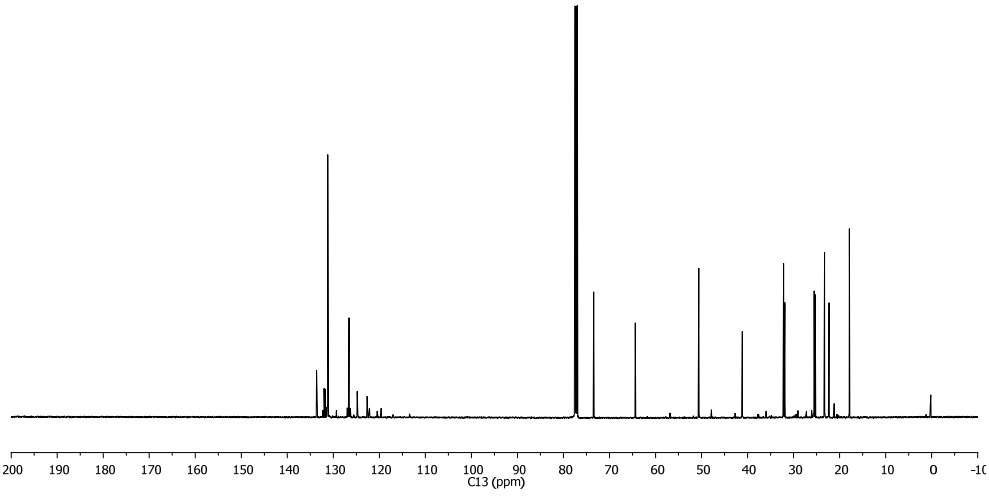
H1 (ppm)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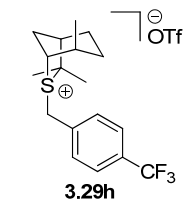
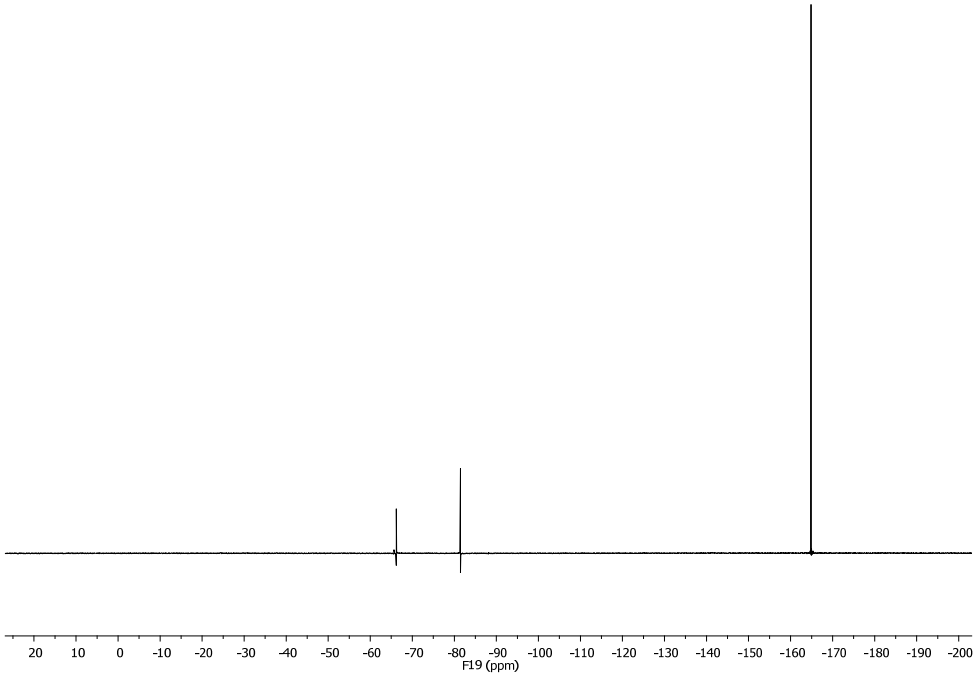
C13 (ppm)


OTf
S
CF3

3.29h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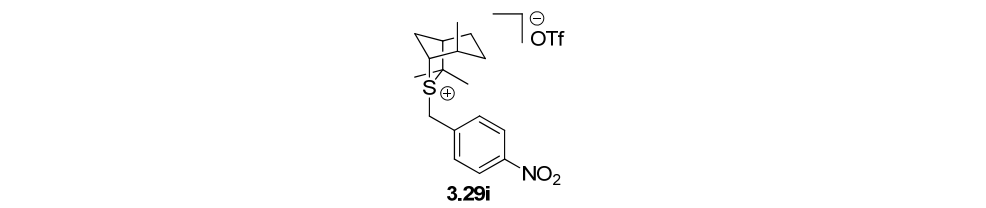
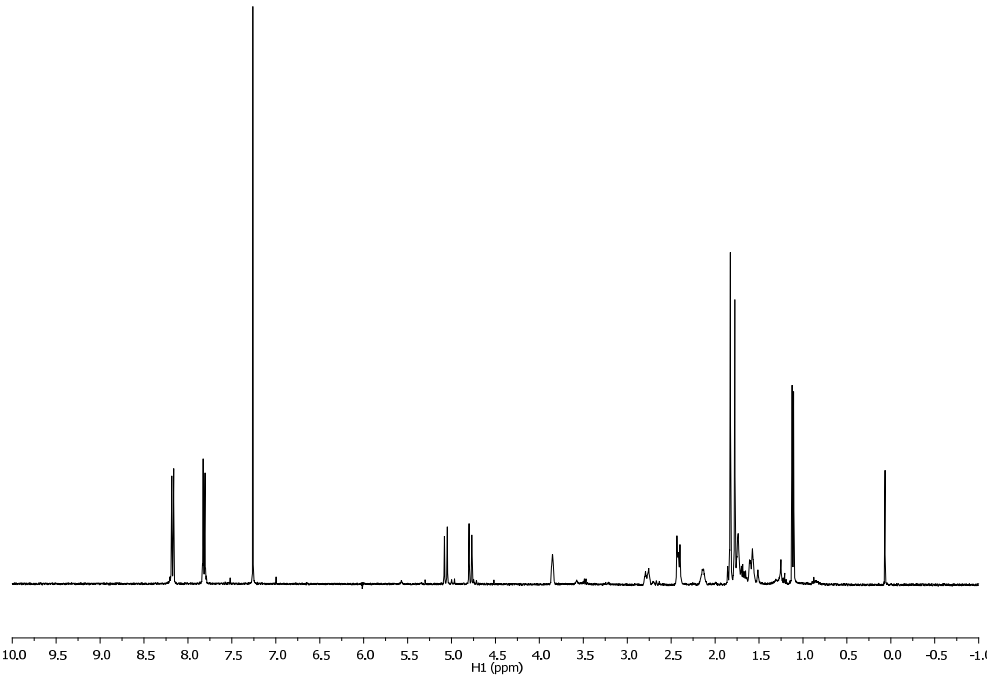

OTf
S
NO2

3.29i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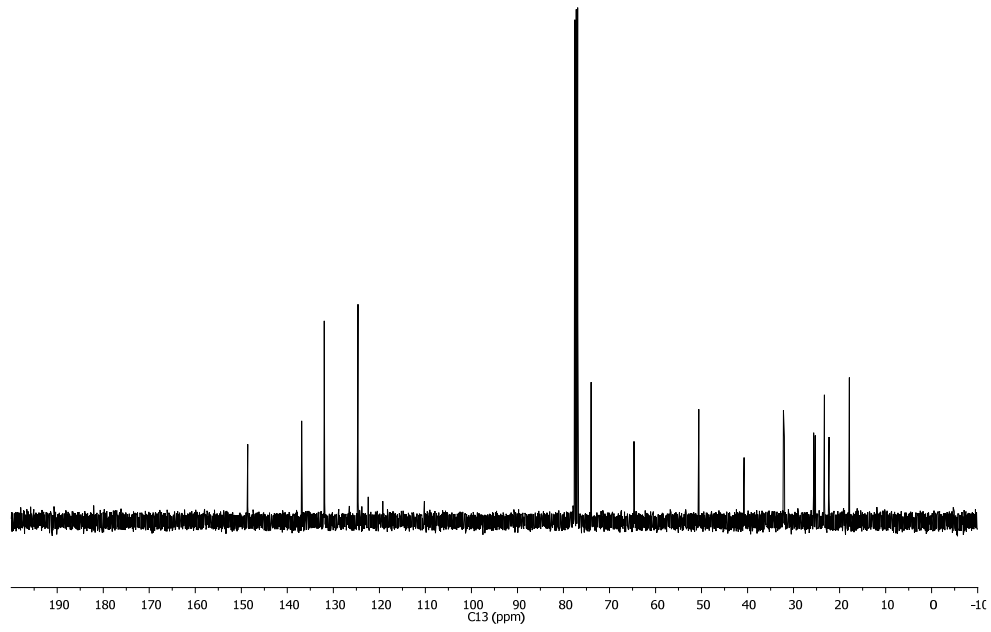
H1 (ppm)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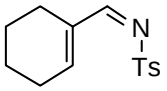
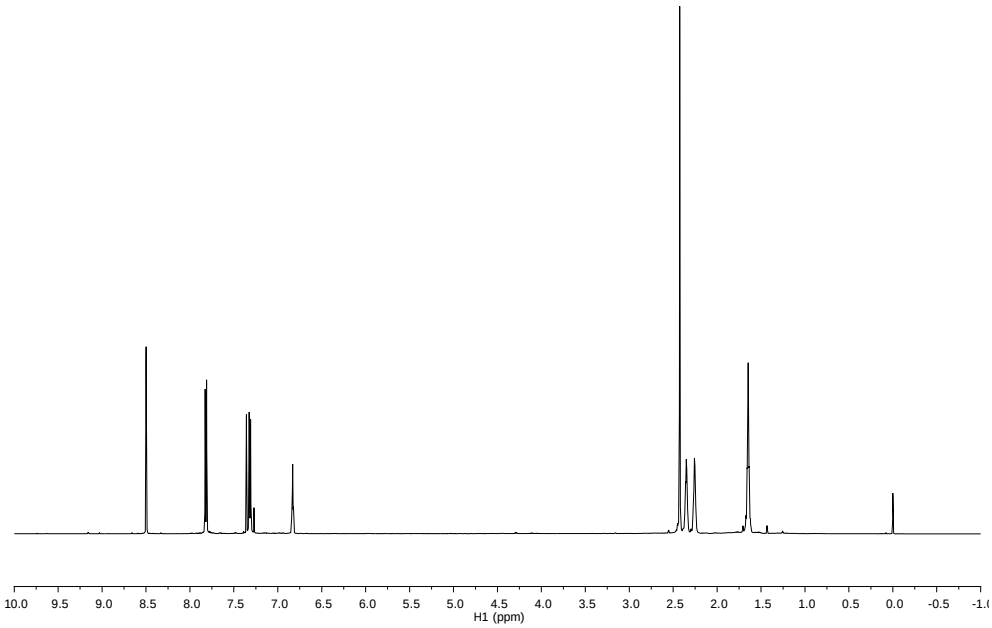
C13 (ppm)


N
Ts

3.28f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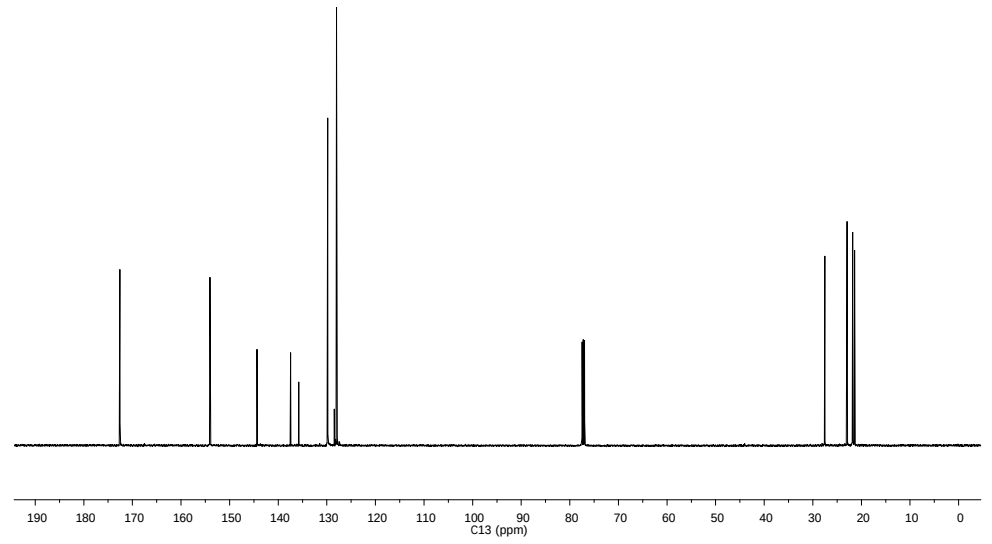
H1 (ppm)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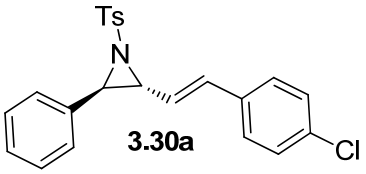
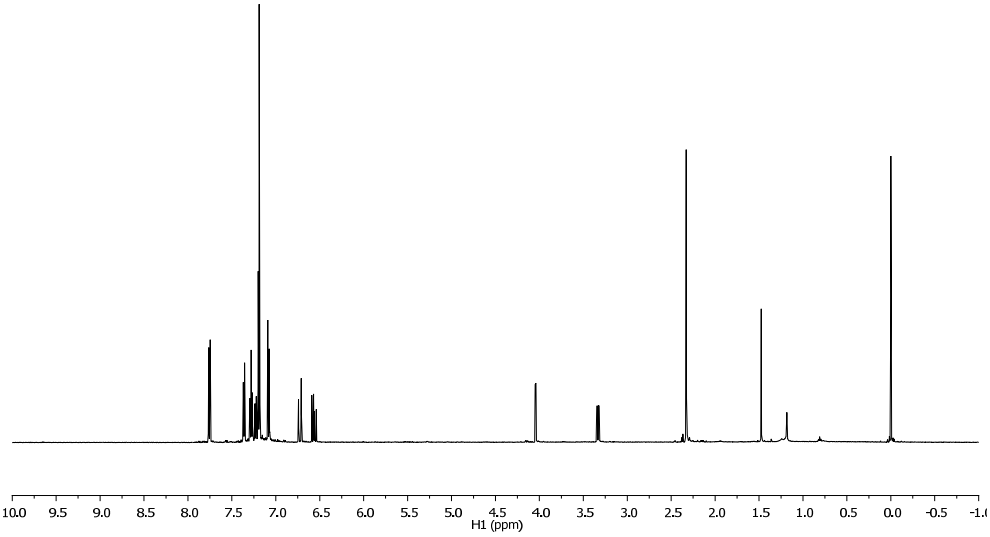
C13 (ppm)


Ts
N
Cl

3.30a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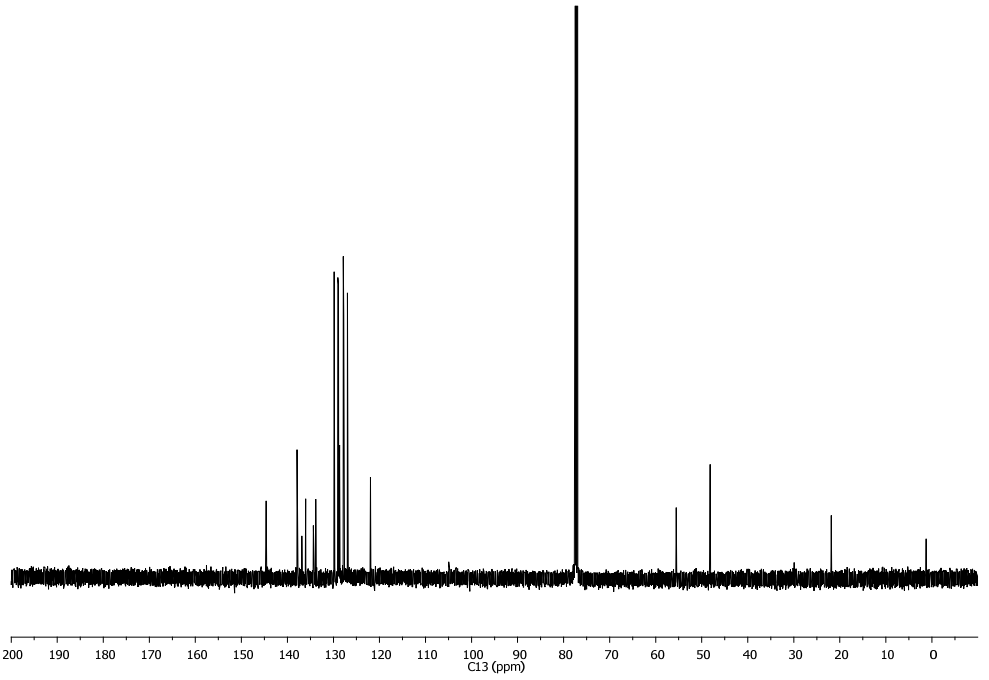
H1 (ppm)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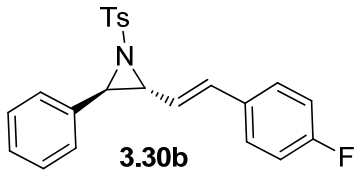
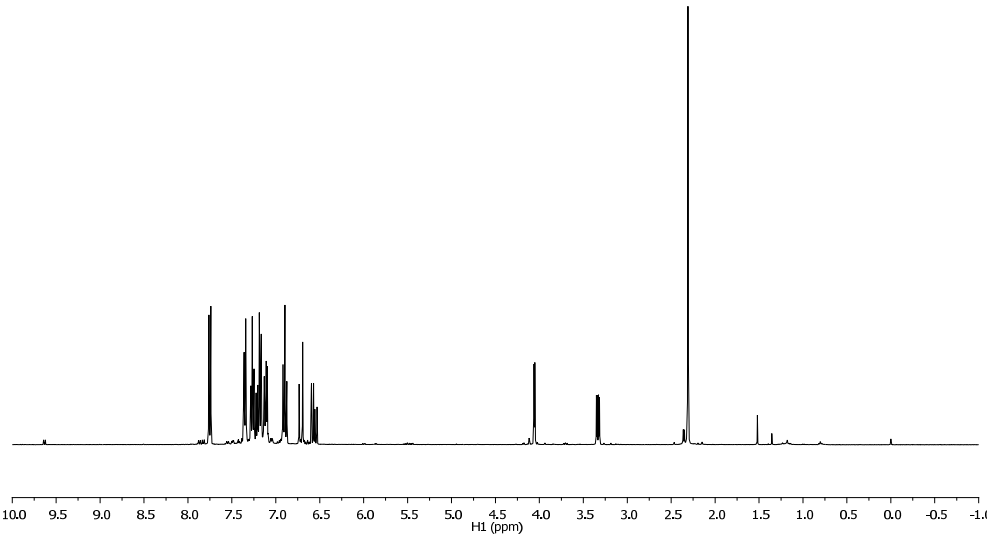
C13 (ppm)


Ts
N
F

3.30b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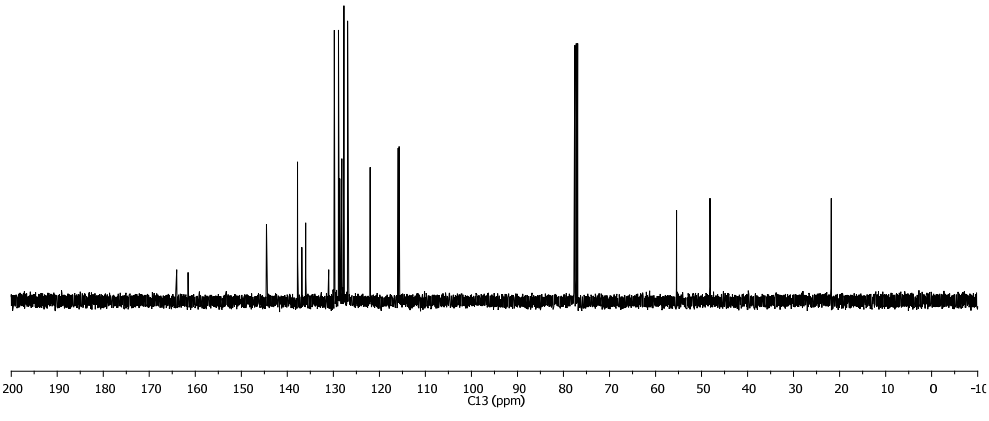
H1 (ppm)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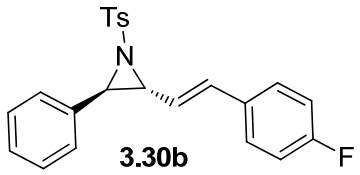
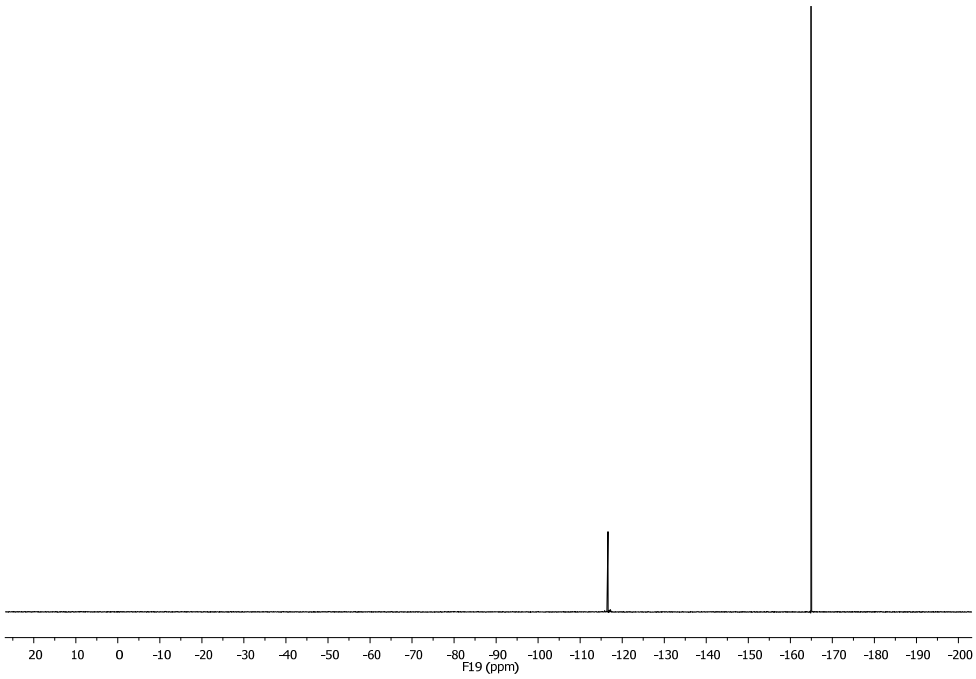
C13 (ppm)


Ts
N
F

3.30b


20
10
0
-10
-20
-30
-40
-50
-60
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-110
-120
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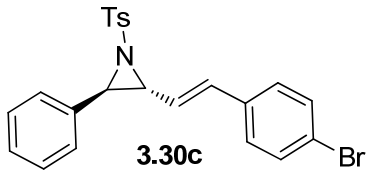
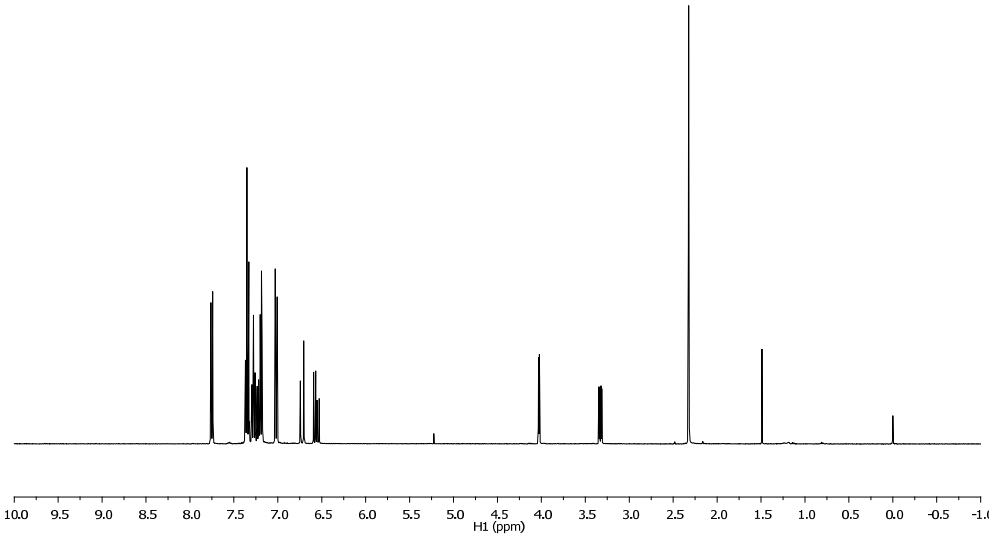
-160
-170
-180
-190
-200
F19 (ppm)


Ts
N
Br

3.30c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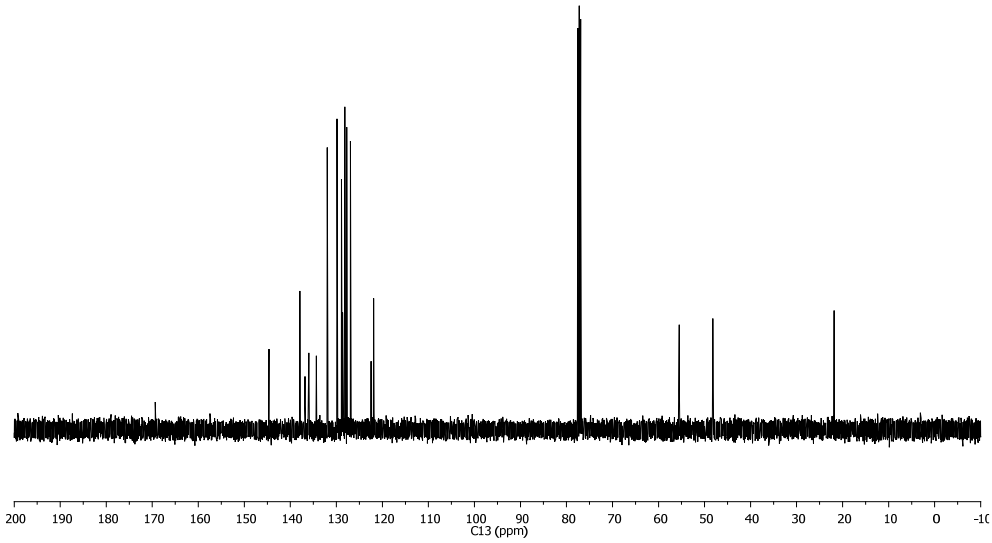
H1 (ppm)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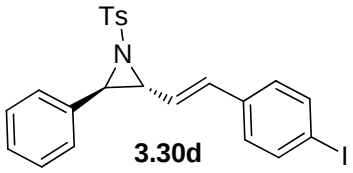
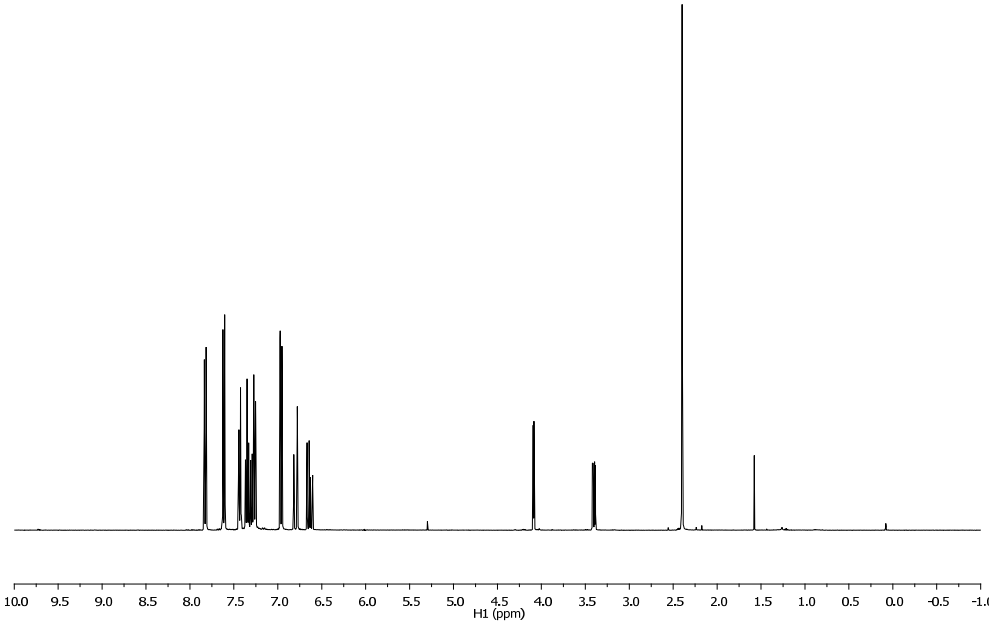
C13 (ppm)


Ts
N
I

3.30d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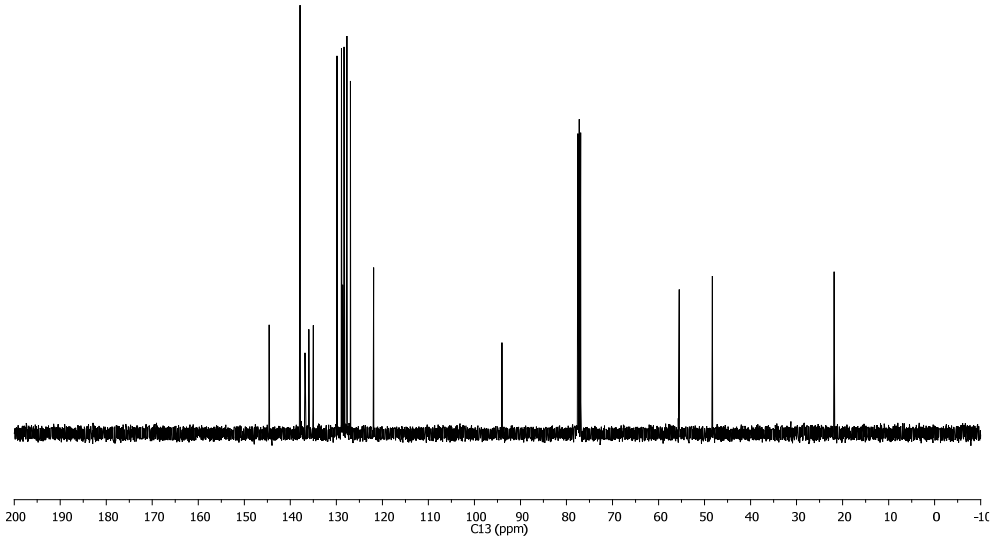
H1 (ppm)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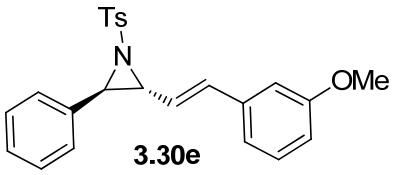
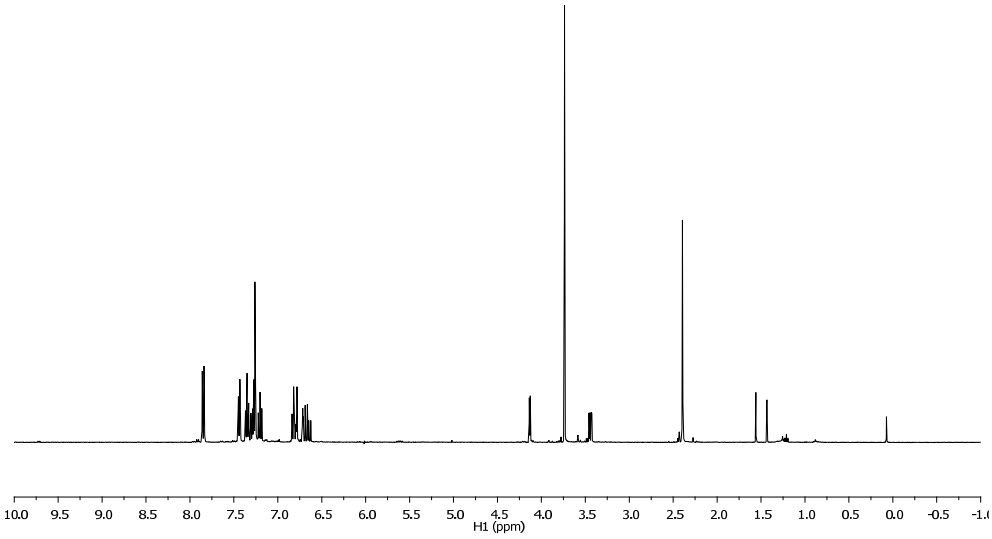
C13 (ppm)


Ts
N
OMe

3.30e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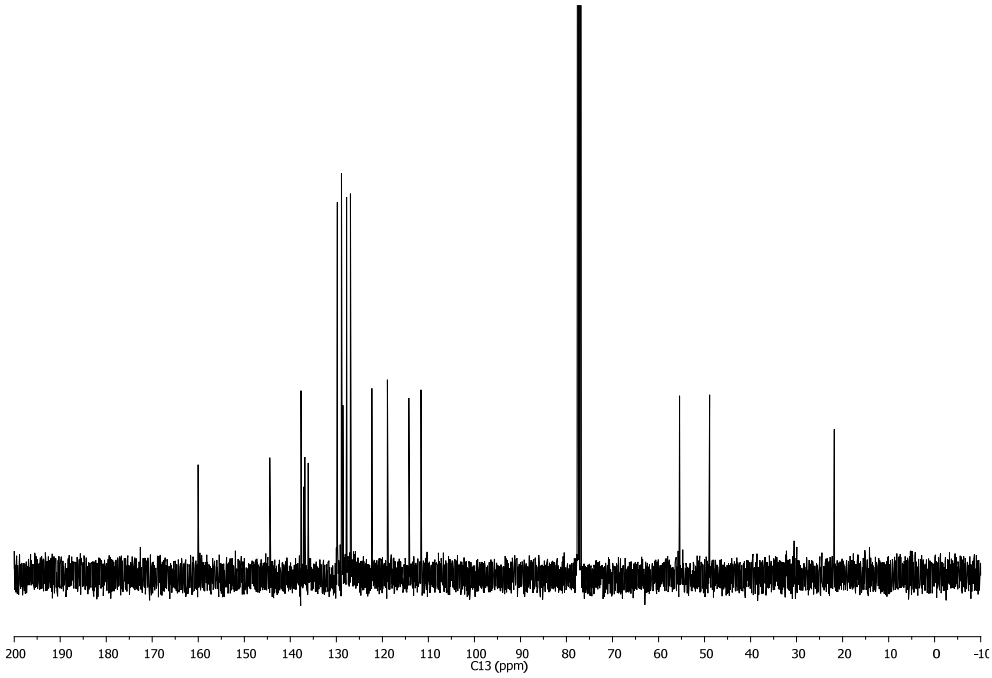
H1 (ppm)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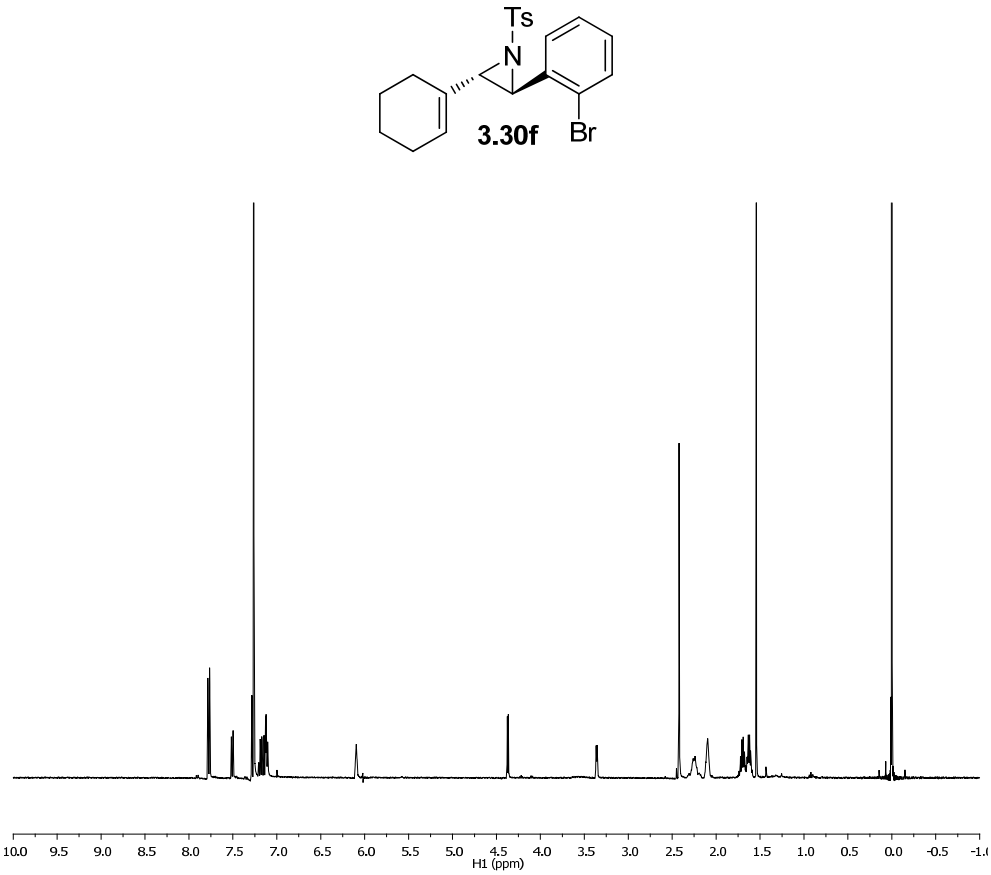
C13 (ppm)


Ts
N
Br
3.30f
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H1 (ppm)
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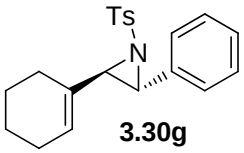
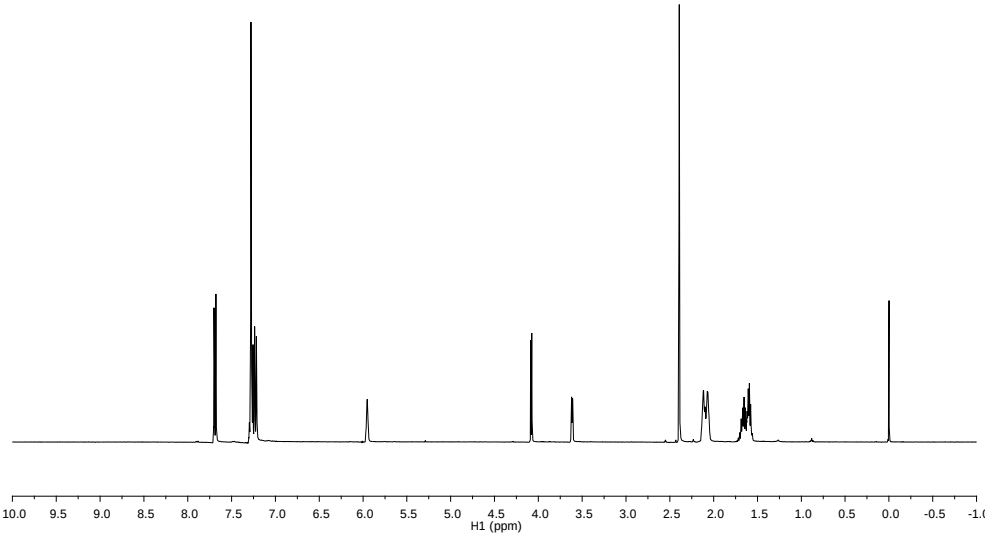
C13 (ppm)


Ts
N

3.30g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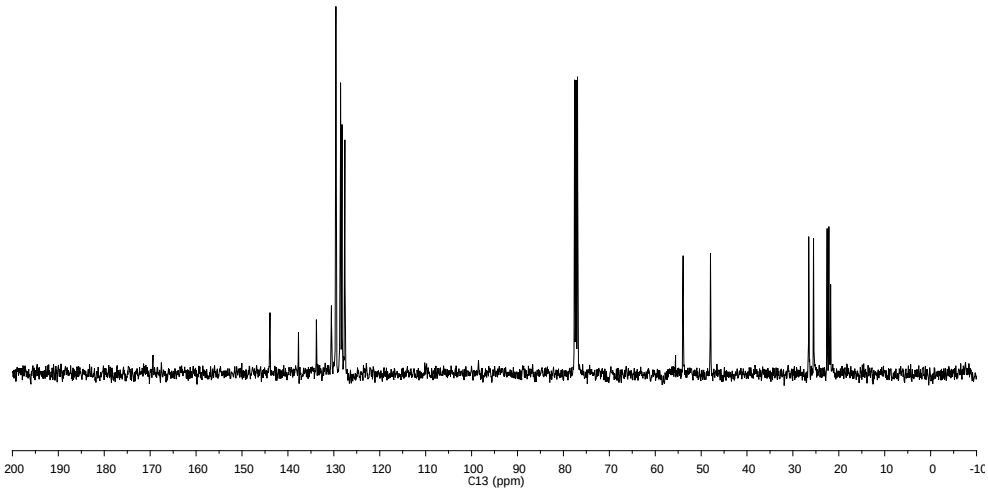
H1 (ppm)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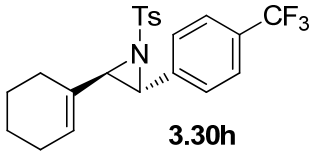
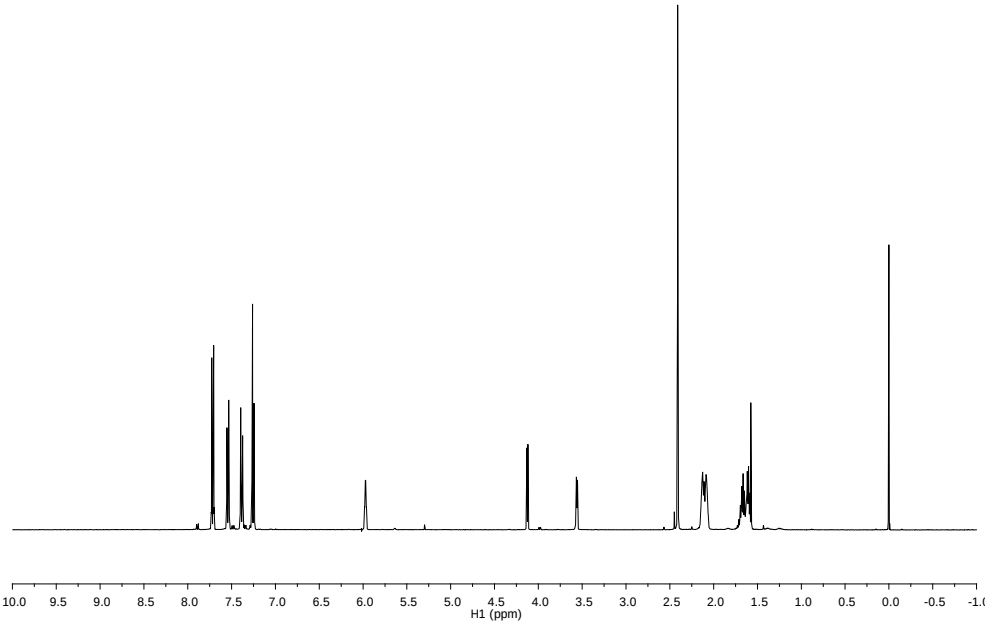
C13 (ppm)


Ts
N
CF3

3.30h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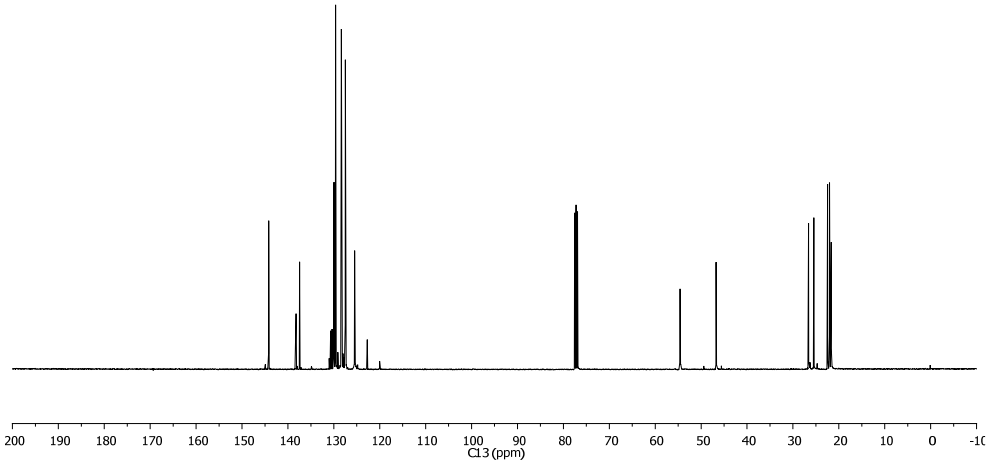
H1 (ppm)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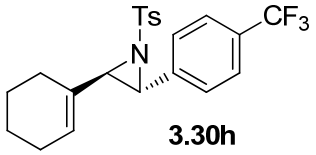
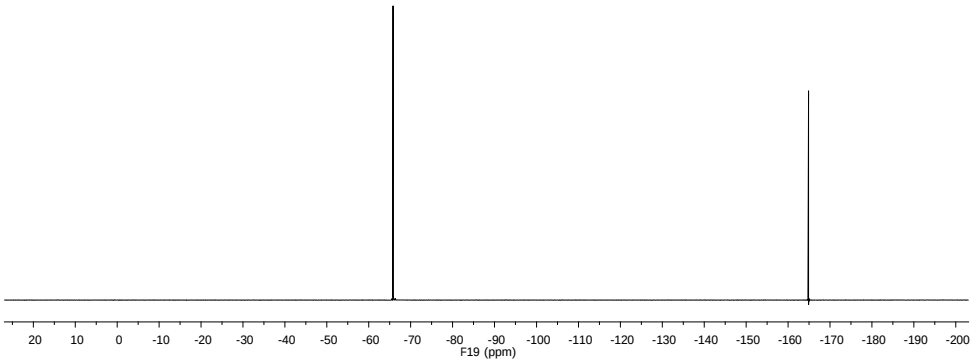
C13 (ppm)


Ts
N
CF3

3.30h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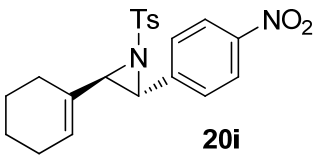
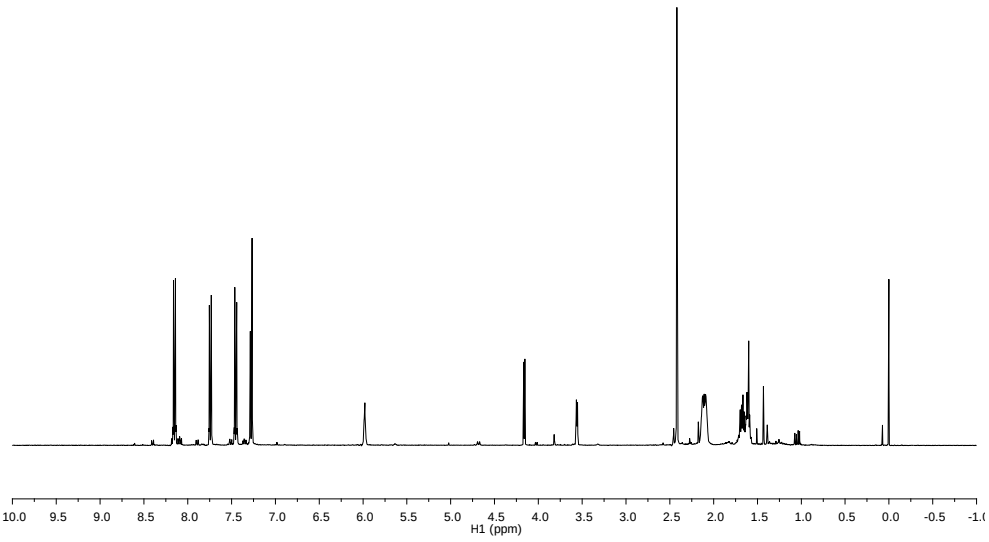
F19 (ppm)


Ts
N
NO2

20i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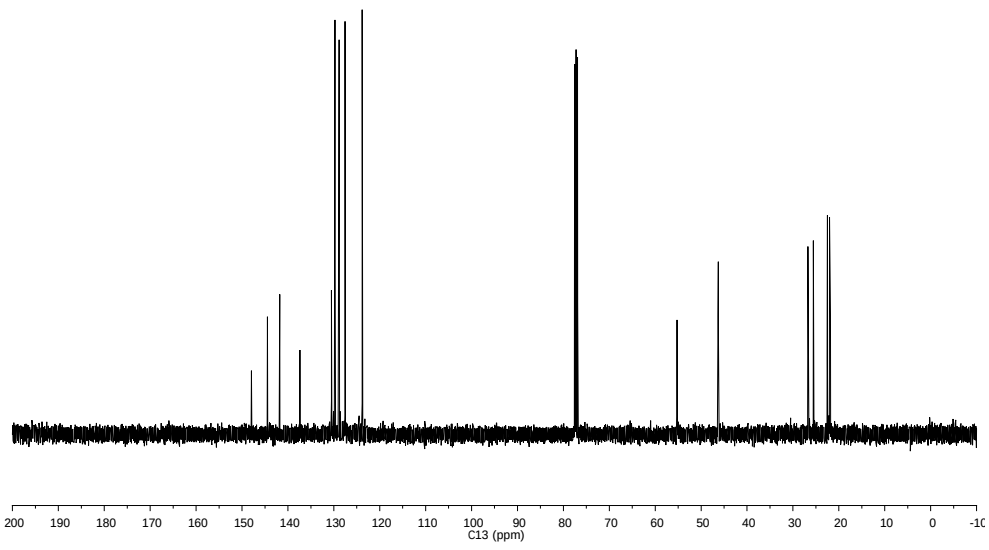
H1 (ppm)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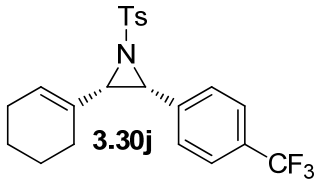
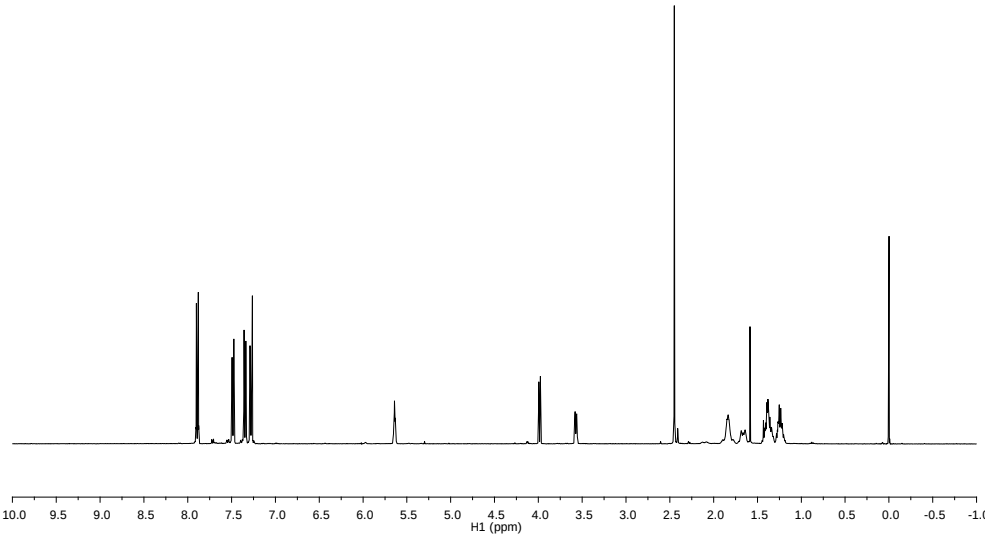
C13 (ppm)


Ts
N
3.30j
CF3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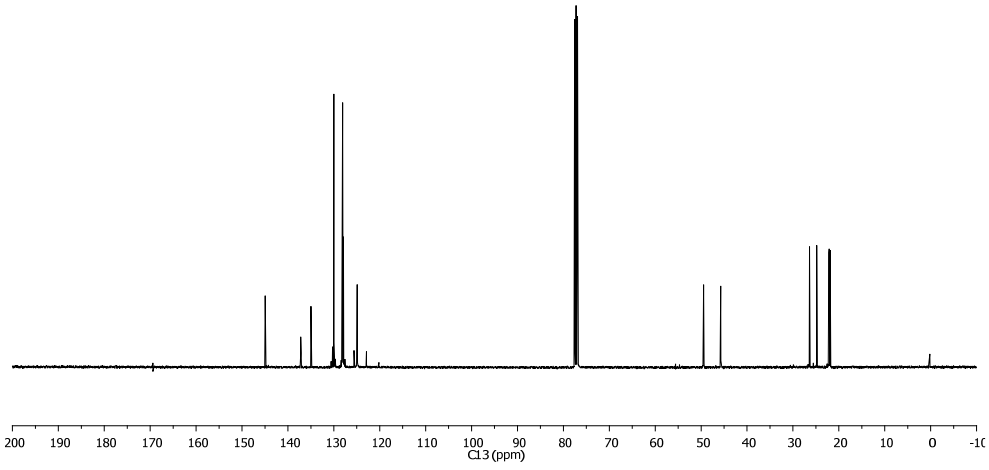
H1 (ppm)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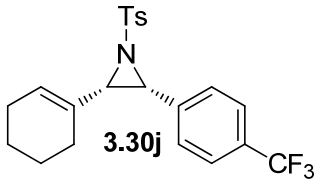
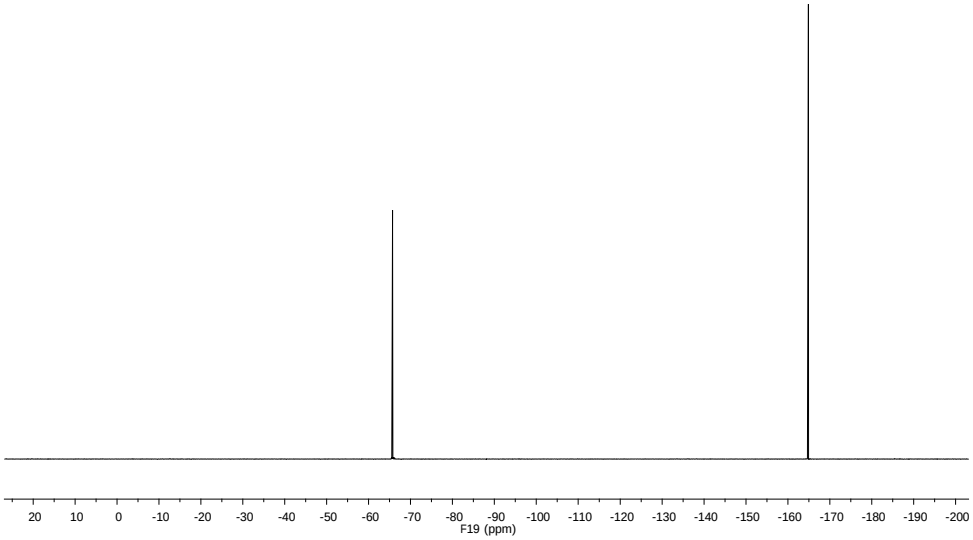
C13 (ppm)


Ts
N
CF3

3.30j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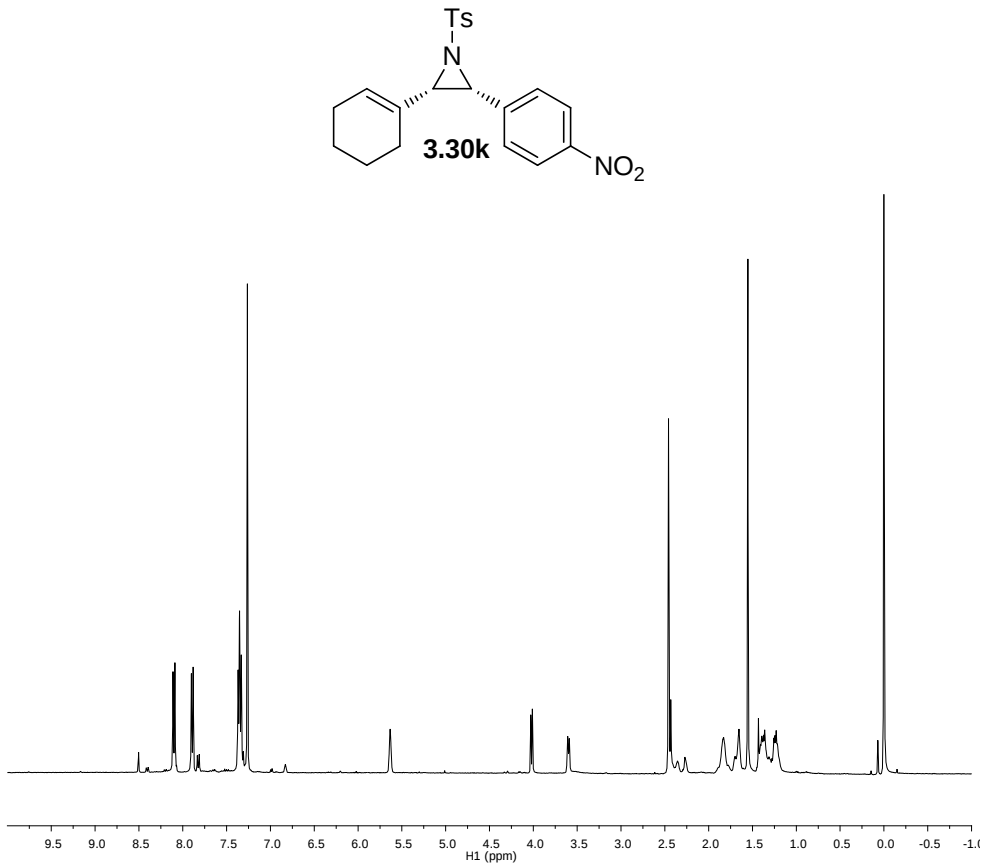
F19 (ppm)


Ts
N
3.30k
NO2
9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
H1 (ppm)
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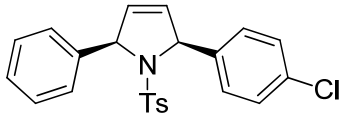
C13 (ppm)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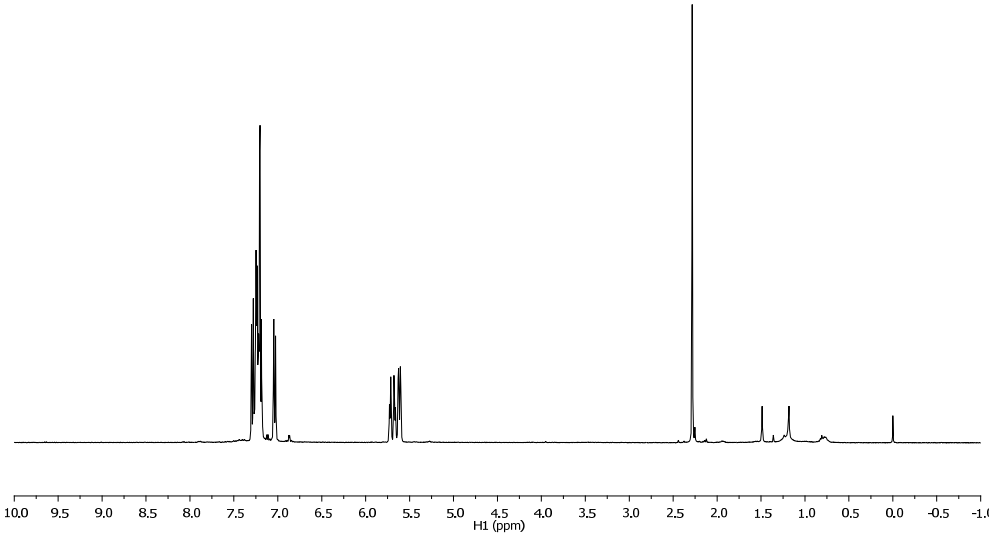
Ts
Cl

3.31a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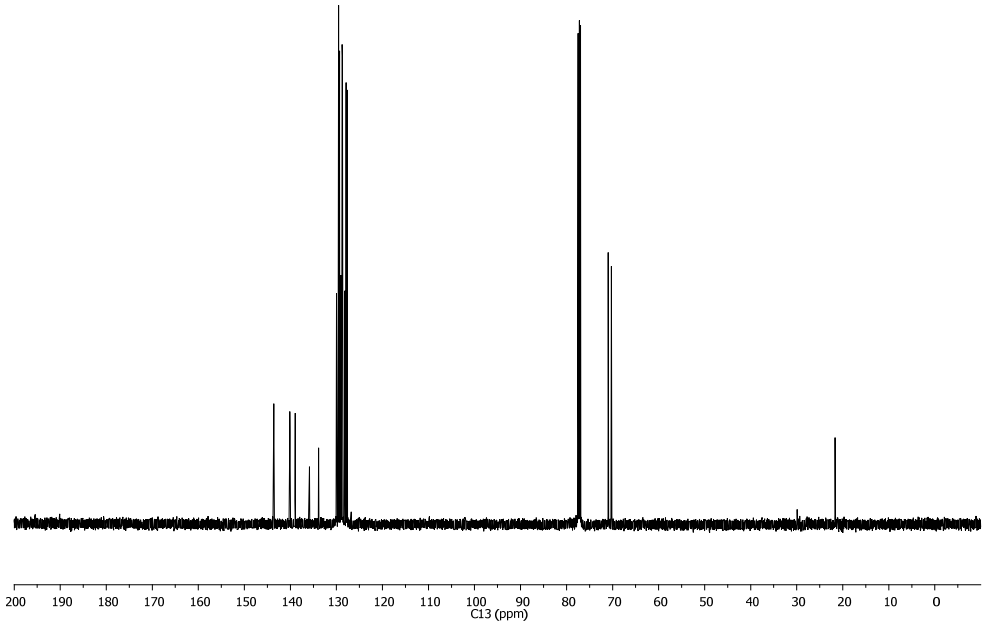
H1 (ppm)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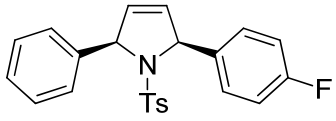
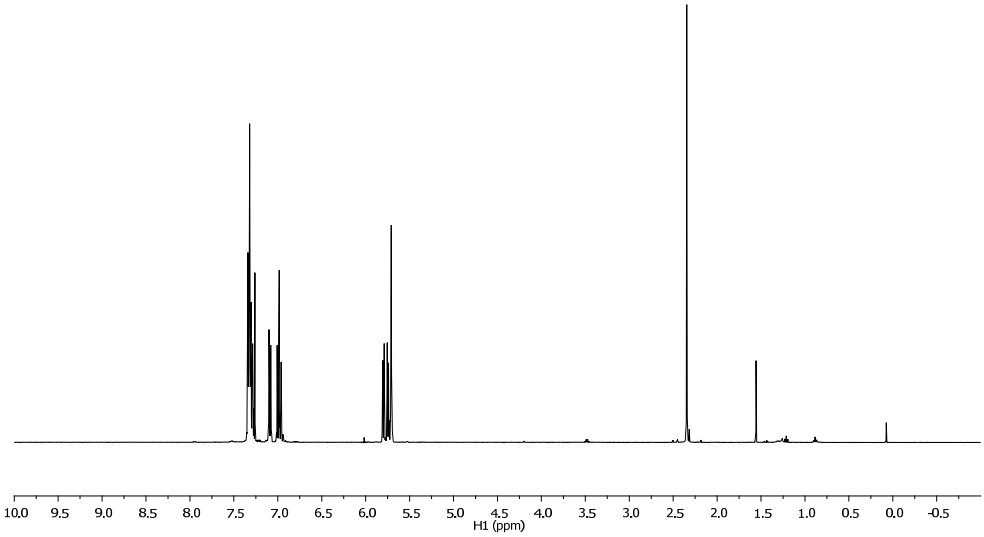
C13 (ppm)


N
Ts
F

3.31b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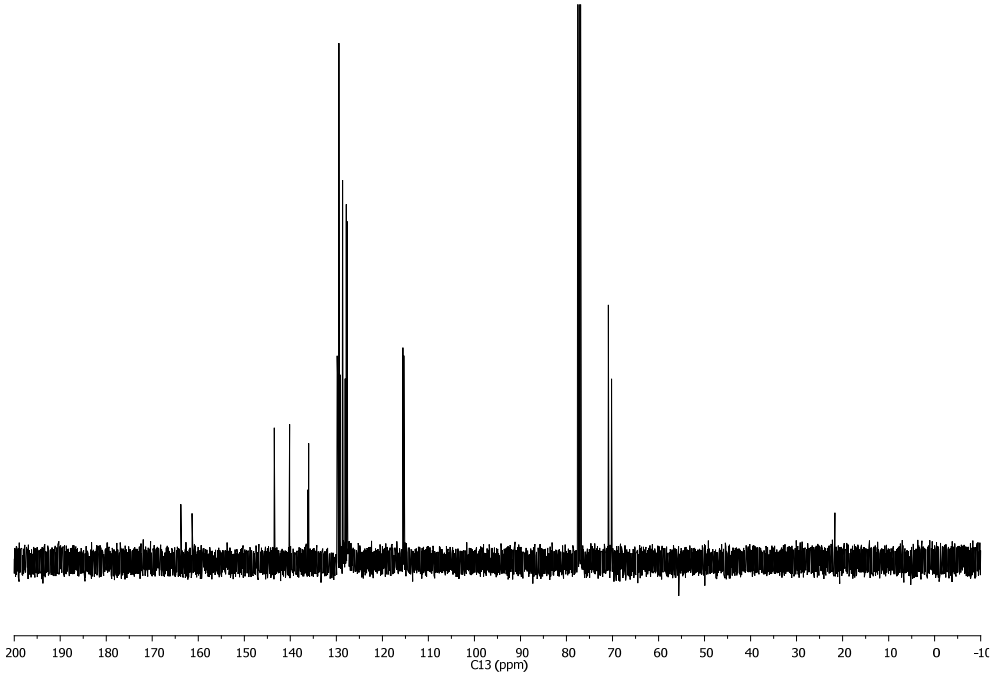
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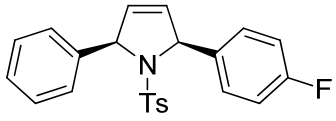
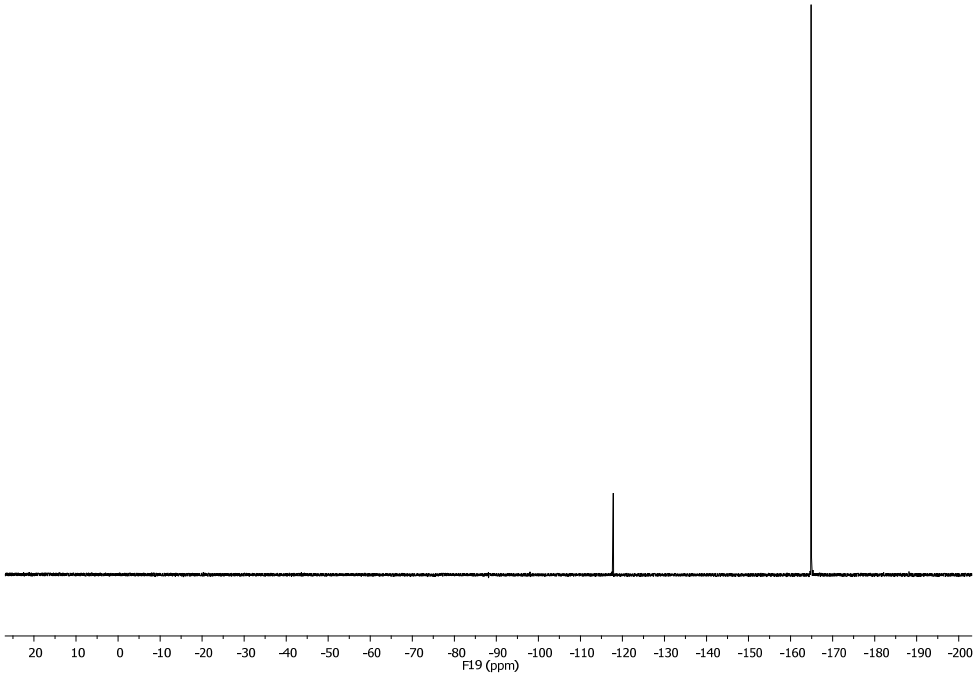

N
Ts
F

3.31b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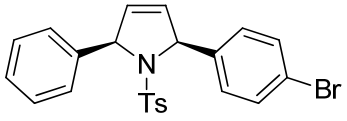
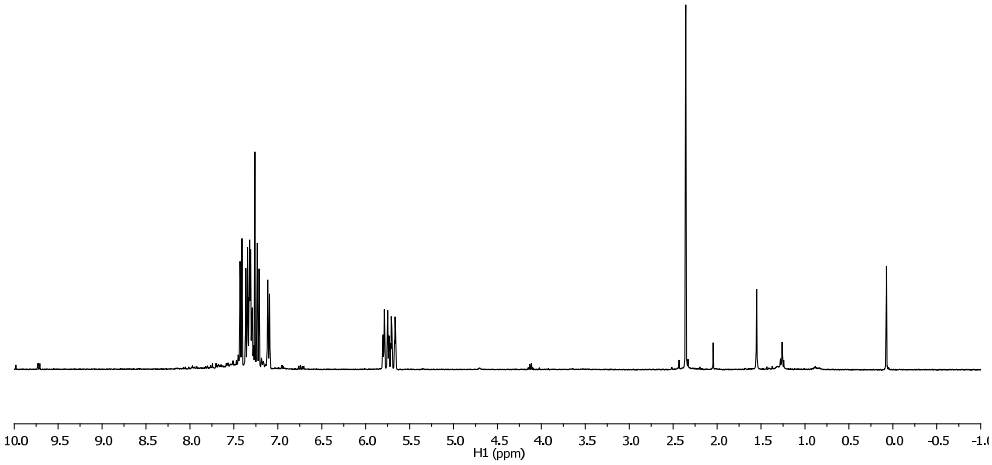

N
Ts
Br

3.31c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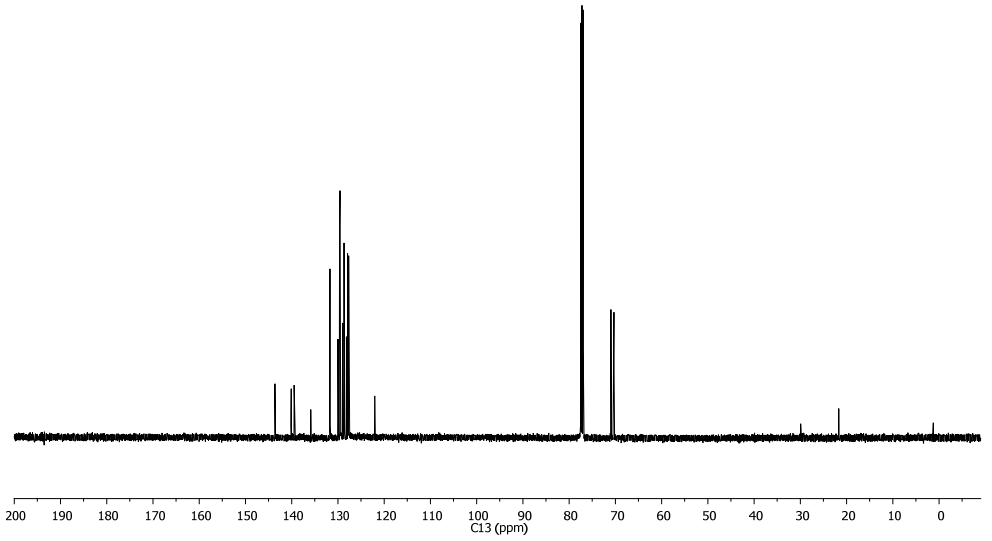
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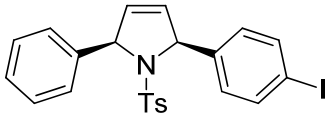
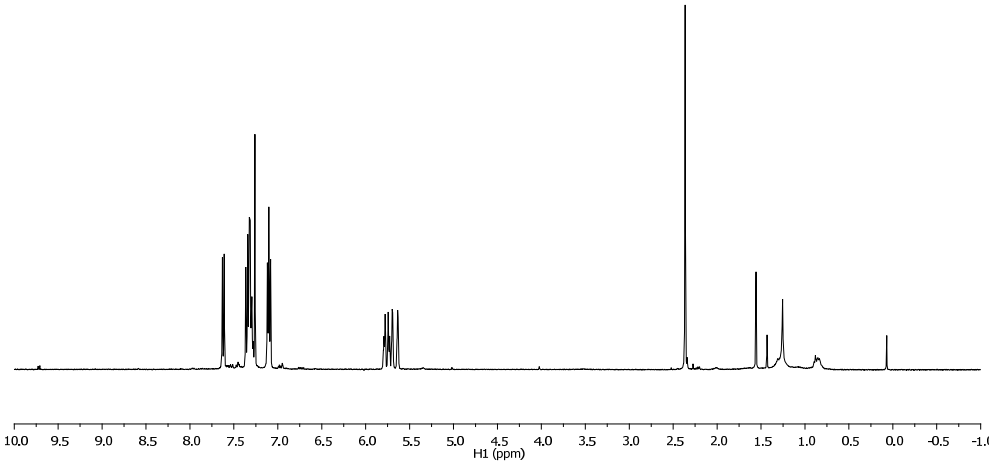

N
Ts
I

3.31d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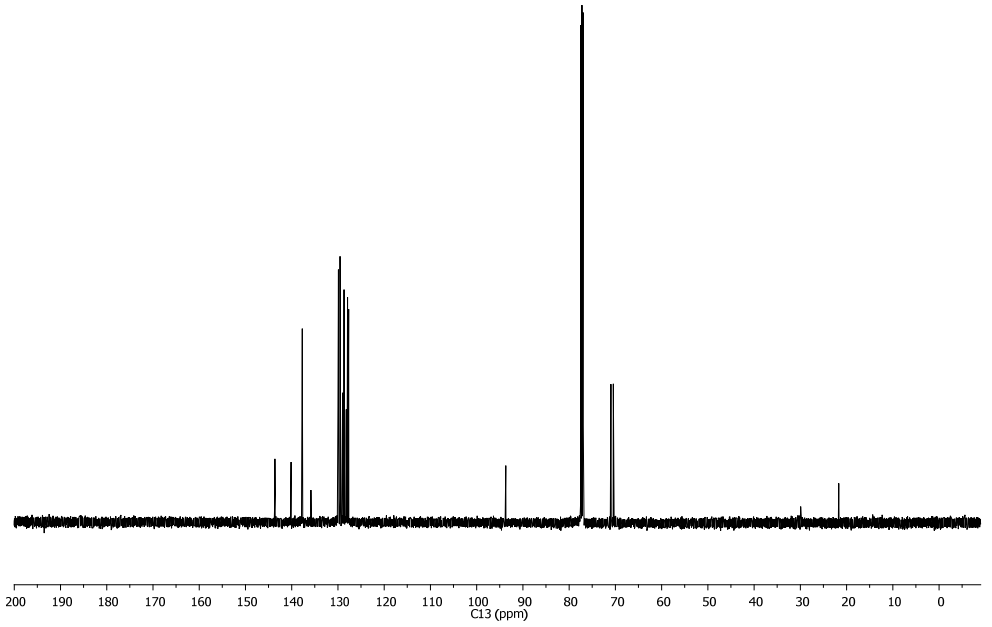
H1 (ppm)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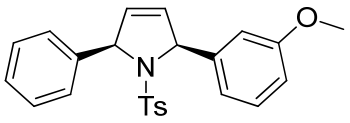
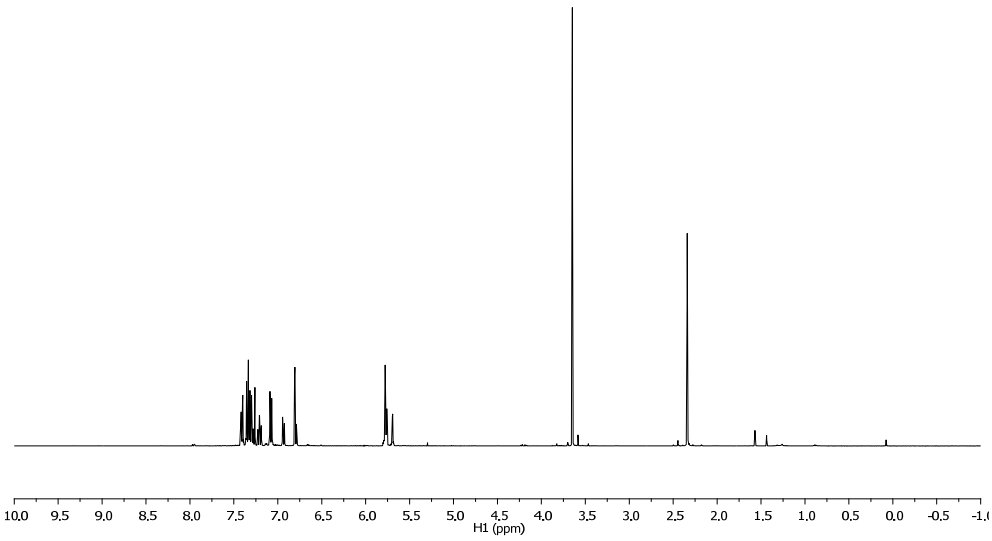

O
N
Ts

3.31e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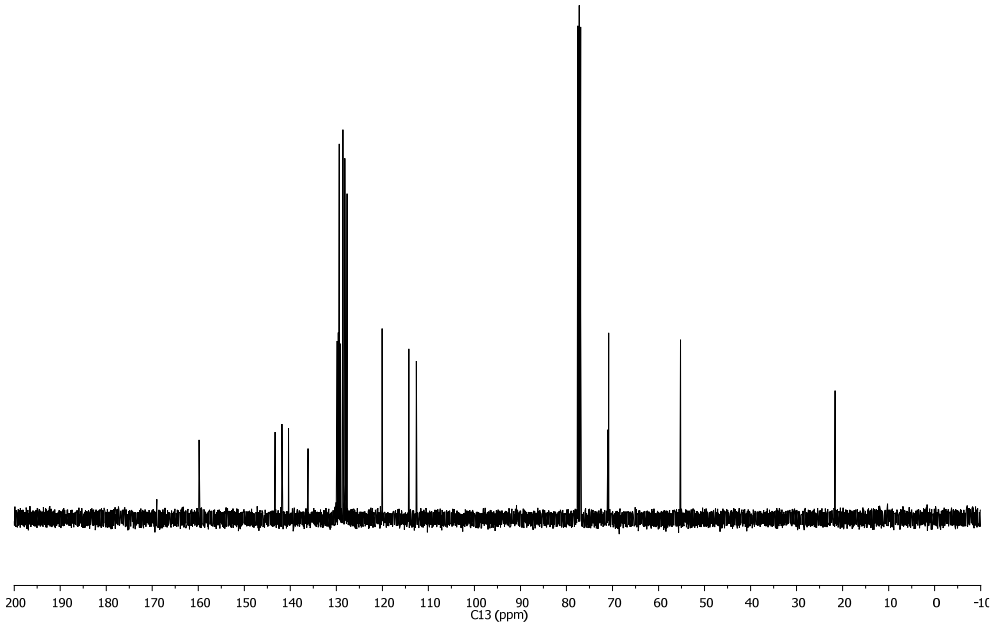
H1 (ppm)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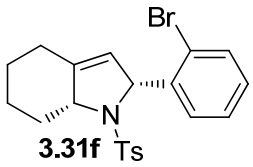
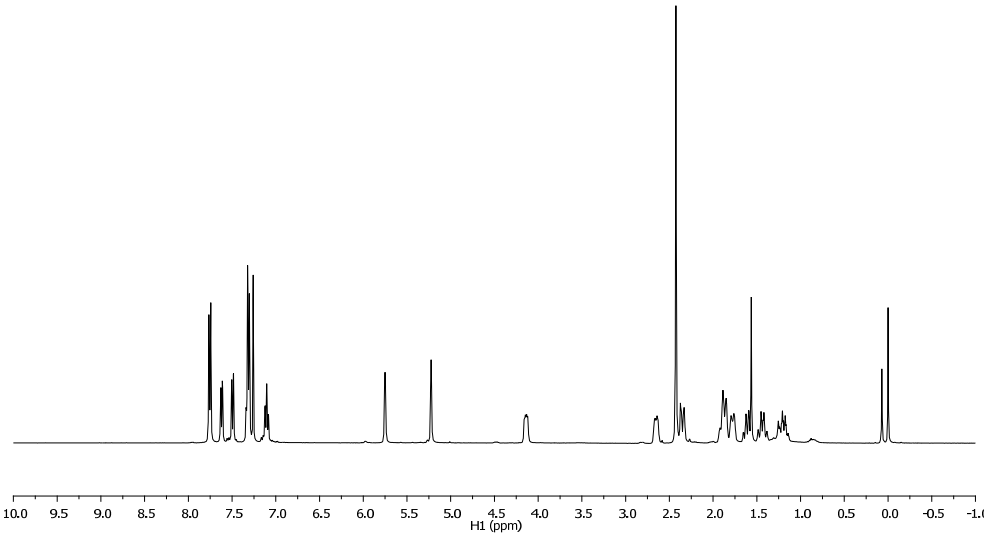
C13 (ppm)


Br
N
Ts

3.31f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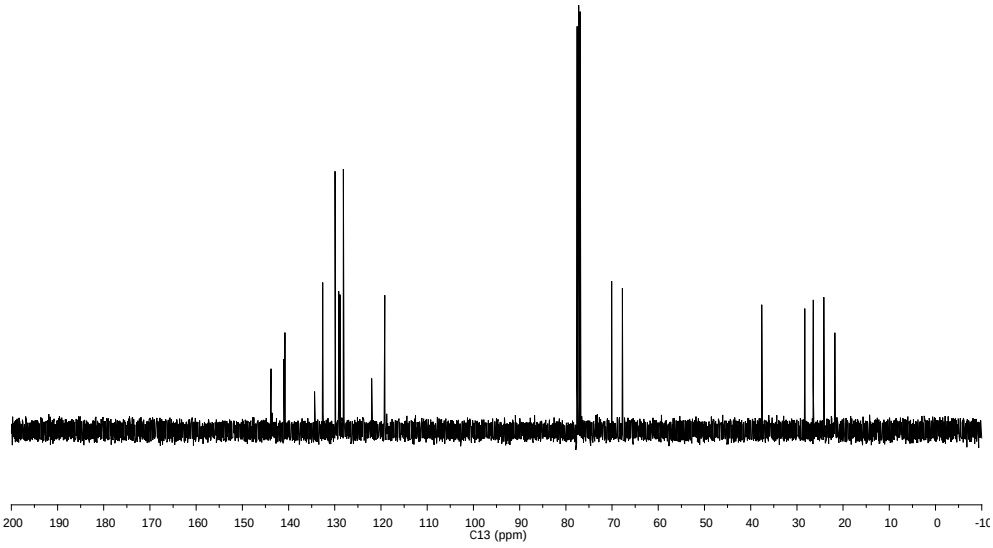
H1 (ppm)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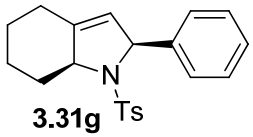
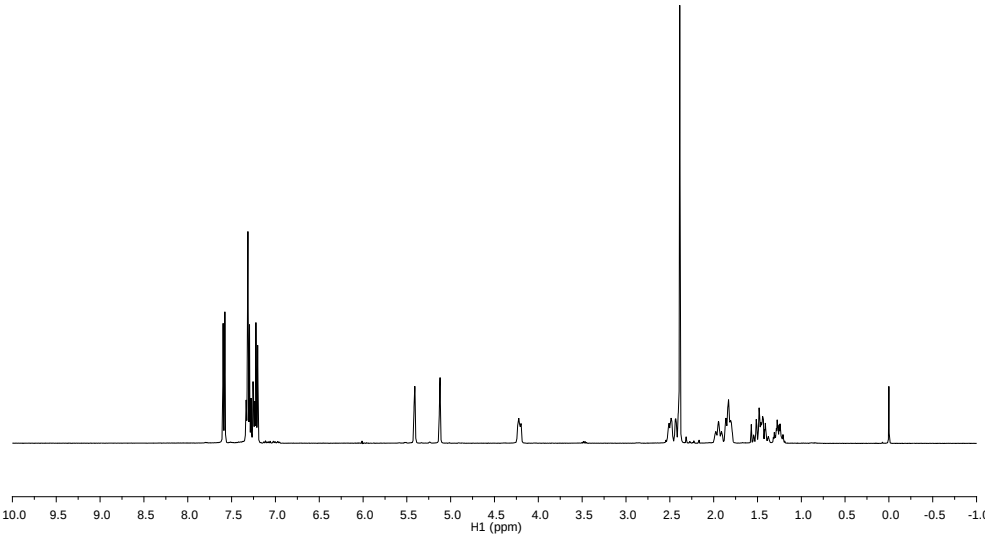
C13 (ppm)


N
Ts

3.31g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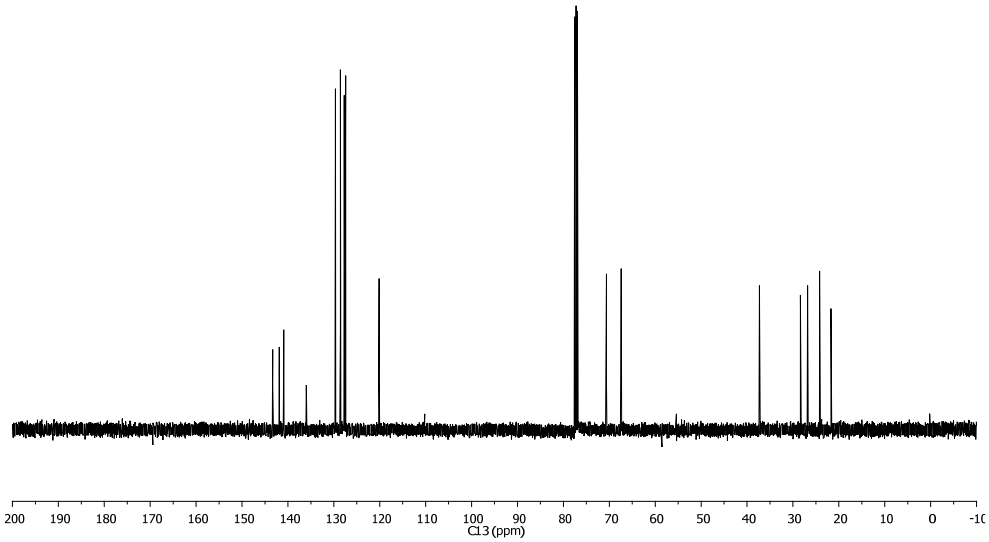
H1 (ppm)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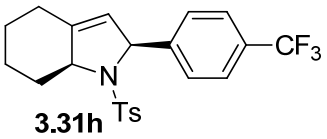
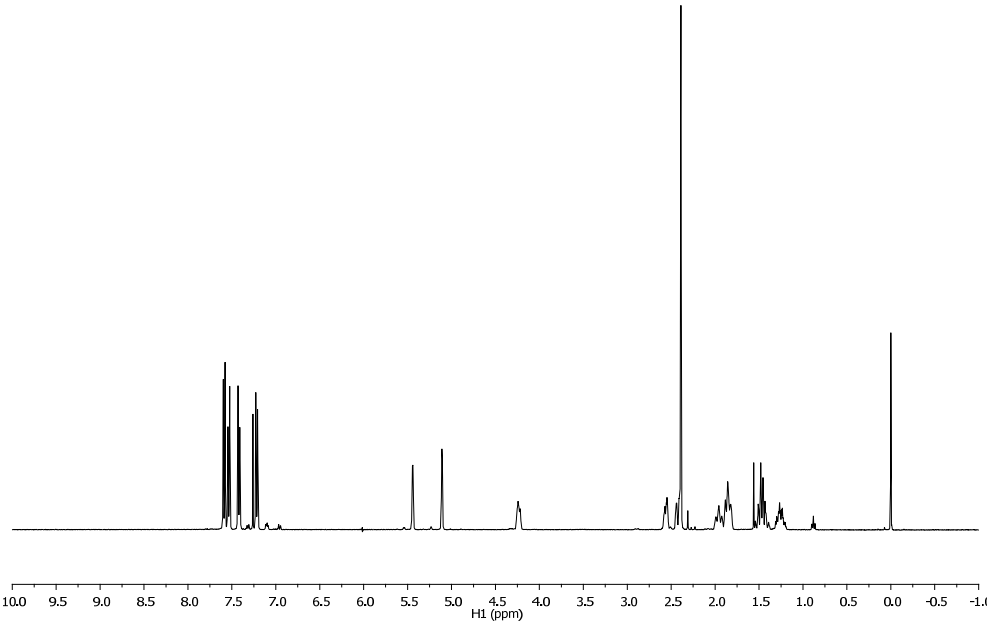

CF3
N
Ts

3.31h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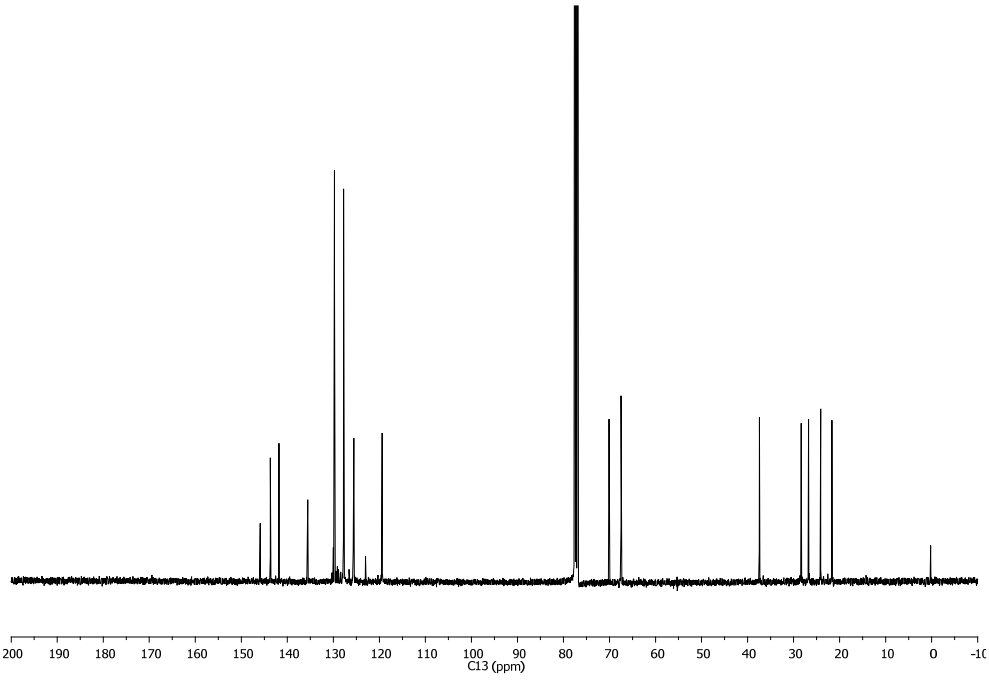
H1 (ppm)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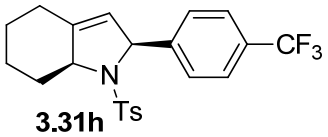
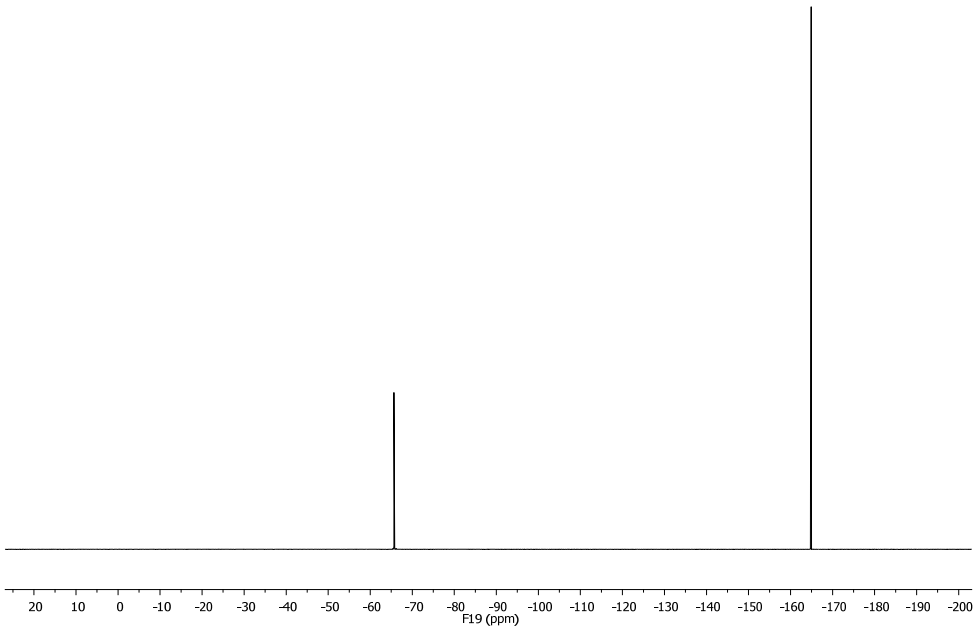

CF3
N
Ts

3.31h


20
10
0
-10
-20
-30
-40
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-60
-70
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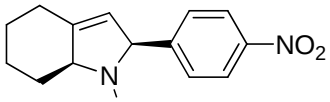
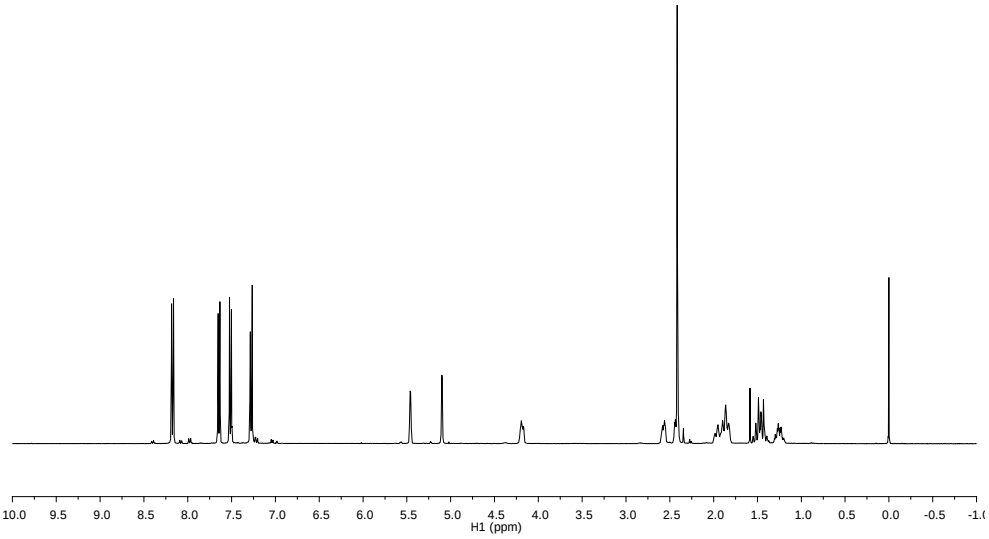
-160
-170
-180
-190
-200
F19 (ppm)


NO2
N
Ts

3.31i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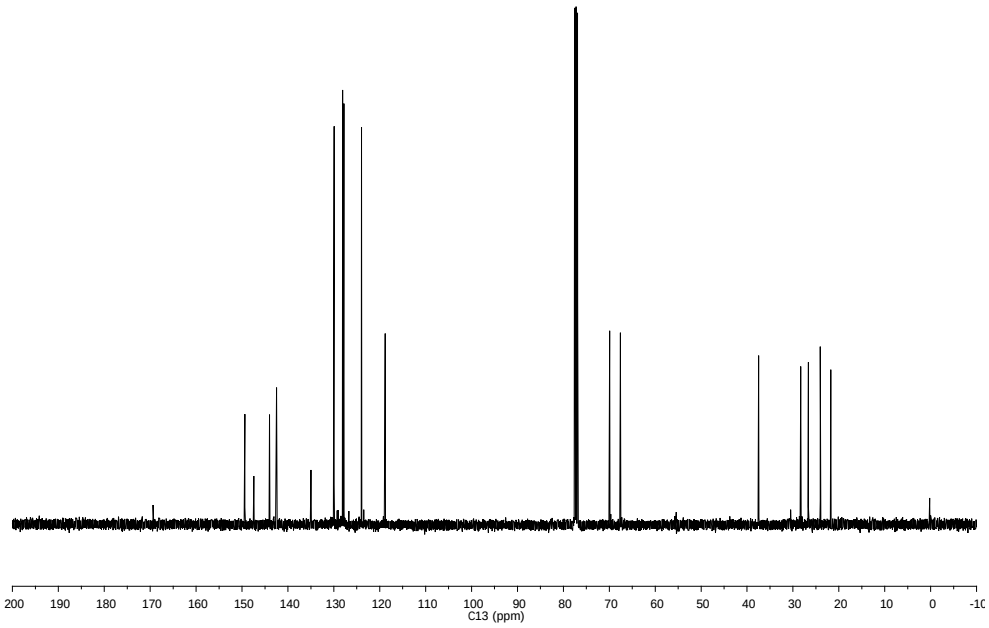
H1 (ppm)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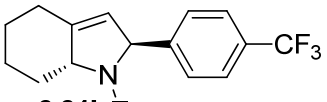
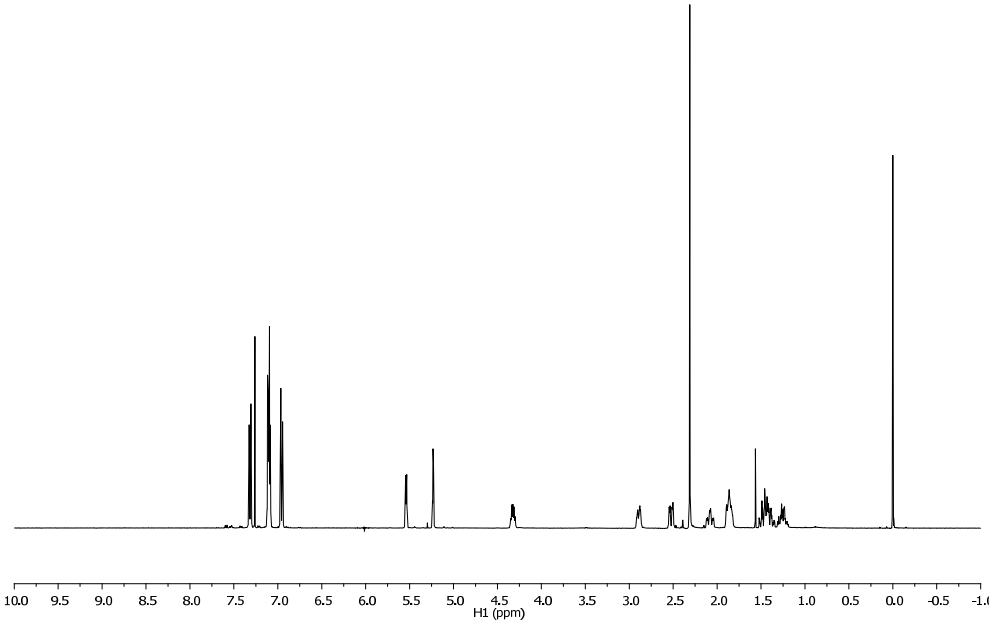

CF3
N
Ts

3.31j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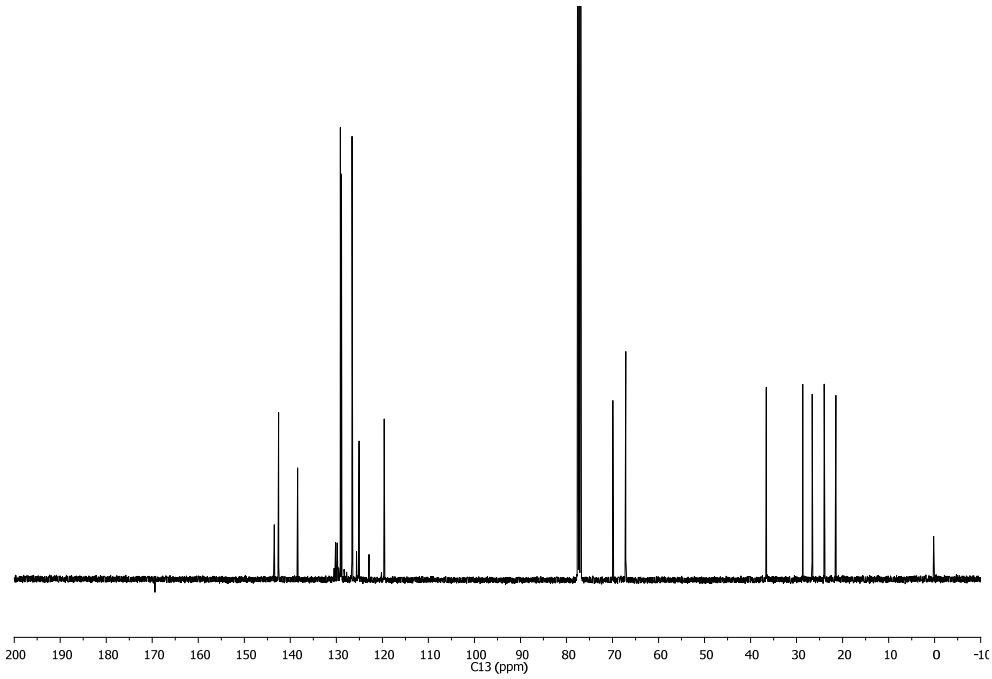
H1 (ppm)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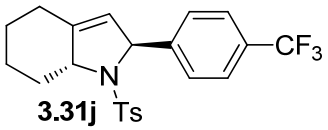
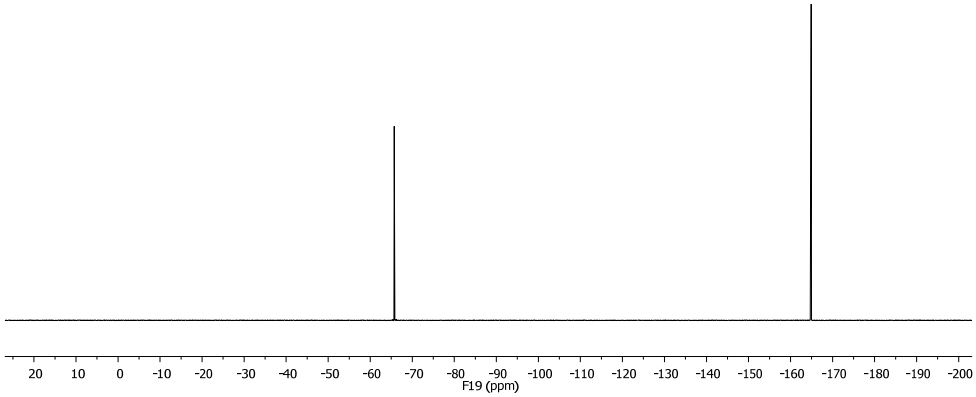

CF3
N
Ts

3.31j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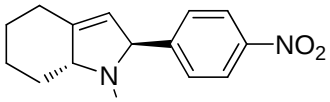
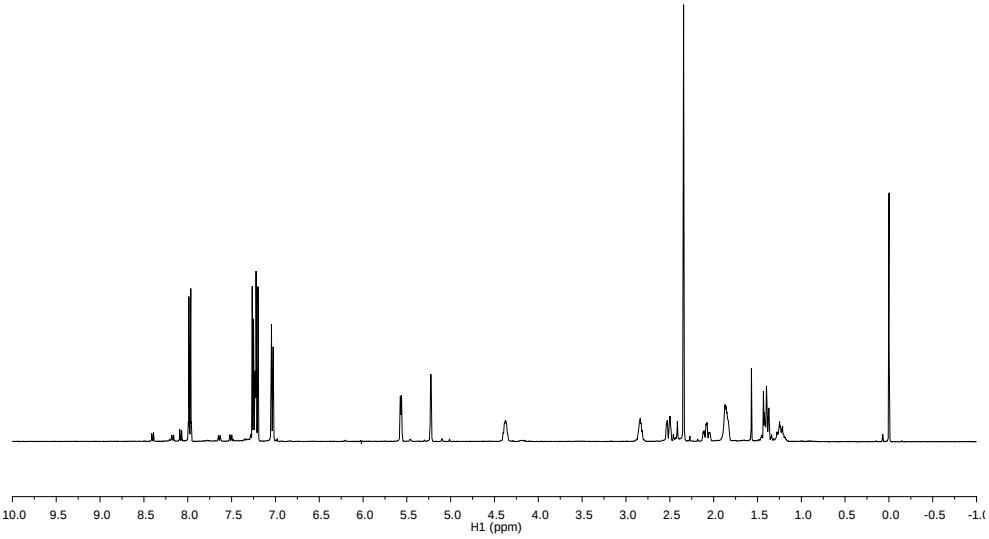
F19 (ppm)


NO2
N
Ts

3.31k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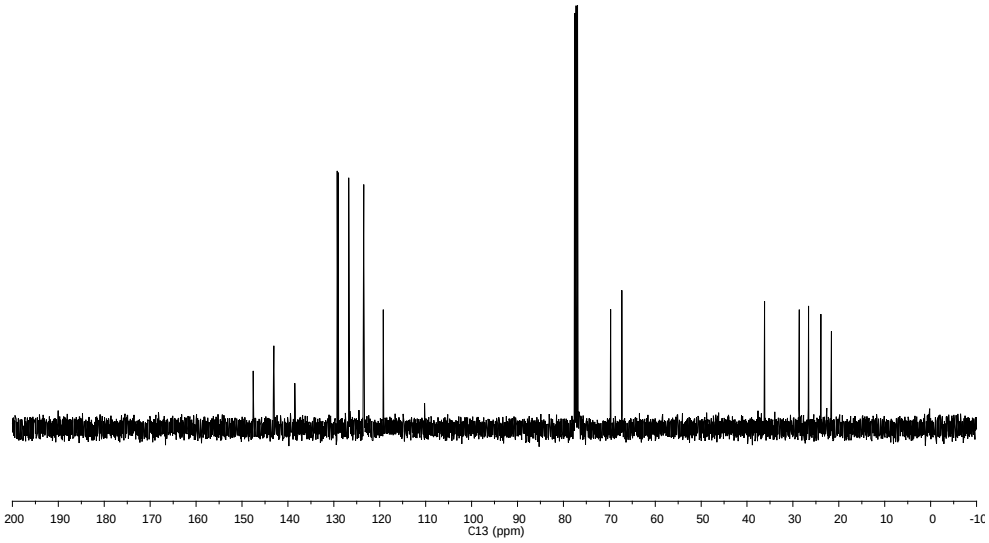
H1 (ppm)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C13 (ppm)

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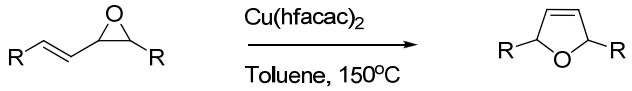
APPENDIX 4

A4.1 Experimental Procedures for Chapter 4

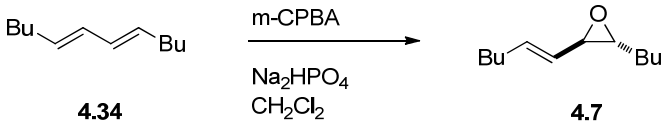
General Information: Commercial reagents were purchased and used without further purification. All glassware was flame dried and reactions were performed under a nitrogen atmosphere, unless otherwise stated. Toluene, benzene, dichloromethane, diethyl ether, and THF were dried over a column of alumina. Flash chromatography was done with Silicycle SiliaFlash® F60 silica, and thin layer chromatography (TLC) was performed with EMD 250 μm silica gel 60-F_{254} plates. ^{1}H and ^{13}C NMR data was acquired on a Varian Inova 400, 500, or 600 (400, 500 or 600 MHz) spectrometer and referenced to residual protic solvent. IR was taken on a Mattson Instruments Research Series FTIR spectrometer. High-resolution mass spectrometry was performed at the University of Illinois at Urbana-Champaign facility. Enantiomeric ratios were determined on an HP 1100 Series HPLC with a Daicel Chiracel® OD-H (0.46 cm x 25 cm) column. GC/MS analysis was performed on an Agilent Technologies 6890N GC with a JW Scientific DB-5ms Column (30 m, 0.25mm thickness, 0.25 μm film thickness) and a JEOL JMS-GCmate II GCMS System. Measurements of optical rotation were done on a Rudolph Research Analytic Autopol III Automatic Polarimeter.

Experimental Information and Characterization Data:



Representative procedure for Vinyl Oxirane Rearrangements: Stock solutions of the epoxide and catalyst in toluene were prepared. To a flame dried 13x100 mm threaded culture tube was added 0.50 mL of the substrate solution (0.144 mmol substrate), followed by 0.50 mL of $Cu(hfacac)_2$ solution (0.0072 mmol catalyst, 5 mol %). The septum was replaced with a cap, and the seal was reinforced with Teflon tape. The tube was put in a 150ºC oil bath. At the end of the reaction, the tube was cooled to room temperature the reaction mixture was filtered through neutral alumina (activity grade 1) washing with EtOAc to remove the copper catalyst. The solvent was removed *in vacuo* and flash chromatography with silica was performed. **Note:** the reaction is highly dependent on catalyst loading and the concentration of starting material.

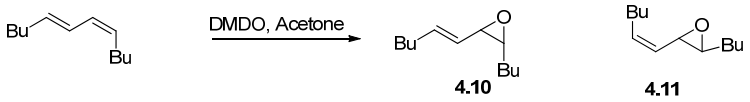
Reaction Analysis: The dihydrofuran:ketone ratio was first determined by NMR analysis on the crude reaction mixture. The diastereoselectivity was then assessed by NMR after removal of $Cu(hfacac)_2$.



4.34 4.7

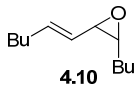
(7E)-trans-5,6-Epoxydodecene (**4.7**)**:** To a 50 mL RBF equipped with a stir bar was added methylene chloride (30 mL), (5*E*,7*E*)-5,7-dodecadiene[1,2] (0.50 g, 3.01 mmol), Na_2HPO_4 (0.742 g, equal mass with m-CPBA), and *m*-CPBA (77%, 0.742 g, 3.31 mmol). After 1 hour, the reaction was cooled to 0°C and filtered through celite. It was then diluted with additional methylene chloride and washed with a saturated $NaHCO_3$ solution (3x), water, and dried over Na_2SO_4. The solvent was removed *in vacuo*, and the product was purified by chromatography (5% Et_2O : 95% pentane) (0.384 g, 67%).

^{1}H NMR (500 MHz, C_6D_6) δ 5.74 (td, *J* = 15.2, 6.8, 1H), 5.21 (tdd, *J* = 15.2, 7.9, 1.4, 1H), 2.97 (dd, *J* = 7.9, 2.0, 1H), 2.65 (ddd, *J* = 6.0, 5.2, 2.1, 1H), 1.99 – 1.82 (m, 2H), 1.48 – 1.09 (m, 10H), 0.89 – 0.72 (m, 6H). **^{13}C NMR** (125 MHz, C_6D_6) δ 135.8, 129.3, 60.4, 58.8, 32.7, 32.6, 31.8, 28.8, 23.2, 22.9, 14.5, 14.4. **IR** (neat) 2958, 2929, 2872, 2860, 1459, 1378, 965 cm^{-1}. **HRMS** (EI^+) *m/z* 182.1670 [calculated mass for $C_{12}H_{22}O$ (M^+) 182.1671].



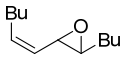
4.10 4.11

(E)-2-Butyl-3-(hex-1-enyl)oxirane (**4.10**)**:** To a 250 mL round bottom flask with a magnetic stir bar was added 0.530 g (3.2 mmol) of (5*Z*,7*E*)-5,7-dodecadiene and 31 ml of acetone. The reaction was cooled to -10°C and 32 mL of dimethyldioxirane[33] (1.0 equiv., ~0.1 M in acetone) was added in 5 mL portions. Reaction was monitored by TLC (5% Et_2O : 95% pentane, $KMnO_4$) until complete and then solvent was evaporated and the product was purified by silica gel chromatography (5% Et_2O : 95% pentane). The products are somewhat unstable to silica gel and separation was tedious but results in 0.362 g of **4.10** and 0.060 g of **4.11** (73% combined yield).



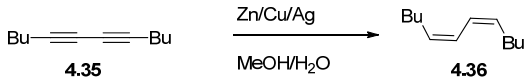
4.10

(E, cis)-2-Butyl-3-(hex-1-enyl)oxirane (**4.10**): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.93 (dt, *J* = 15.4, 7.1, 1H), 5.39 – 5.20 (m, 1H), 3.37 (dd, *J* = 8.1, 4.3, 1H), 3.05 (ddd, *J* = 6.6, 5.6, 4.4, 1H), 2.09 (dt, *J* = 8.2, 4.1, 2H), 1.66 – 1.53 (m, 2H), 1.53 – 1.44 (m, 2H), 1.44 – 1.26 (m, 6H), 0.98 – 0.83 (m, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.3, 124.3, 59.1, 57.4, 32.5, 31.4, 28.7, 27.9, 22.8, 22.4, 14.2, 14.1. **IR** (neat) 2955, 2926, 2868, 1464, 1326, 1280, 1152, 752 cm^{-1}. **HRMS** (EI^+) m/z 182.16692 [calculated mass for $C_{12}H_{22}O$ (M^+) 182.16707].



4.11

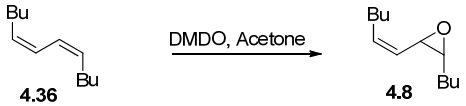
(Z, trans)-2-Butyl-3-(hex-1-enyl)oxirane (**4.11**): Previously synthesized but not characterized[4]. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 5.70 (dt, *J* = 11.0, 7.7, 1H), 5.14 – 4.95 (m, 1H), 3.35 (dd, *J* = 8.9, 2.3, 1H), 2.82 (td, *J* = 5.7, 2.3, 1H), 2.32 – 2.10 (m, 2H), 1.67 – 1.52 (m, 2H), 1.52 – 1.24 (m, 8H), 0.95 – 0.88 (m, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 136.4, 127.1, 60.2, 54.5, 31.7(7), 31.7(9), 28.1, 27.4, 22.5, 22.2, 14.0, 13.9. **IR** neat 2958, 2930, 2860, 1459, 1379, 1304, 929, 872 cm^{-1}. **HRMS** (EI^+) m/z 181.1590 [calculated mass for $C_{12}H_{21}O$ (M-H) 181.1592].



4.35 **4.36**

(Z,Z)-Dodeca-5,7-diene (**4.36**): Method adapted from known protocol.[5] To a 25 mL flame dried flask was added a stir bar and 8 g of Zn dust. Under N_2 atmosphere was added 6 mL of H_2O followed by 0.8 g $Cu(OAc)_2 \cdot H_2O$ (4.0 mmol, 1.6 equiv.). After 15 minutes of stirring 0.8 g of $AgNO_3$ (4.7 mmol, 1.9 equiv.) was added. The solution was stirred for 30 minutes and then filtered under vacuum and the solid was washed with water (2 x 20 mL), methanol (2 x 20 mL), acetone (2 x 20 mL), and finally Et_2O (2 x 20 mL). The solid Zn was transferred into a 50 mL round bottom flask under N_2. To this flask were added 10 mL of MeOH and 10 mL of H_2O. Then dodeca-5,7-diyne[6] 0.413 g (2.5 mmol) was added in a solution of methanol and heterogeneous reaction was stirred for 7 days at room temperature. Then the solution was filtered through celite and washed with MeOH. The filtrate was extracted with hexanes and the organic layer dried with Na_2SO_4. The solvent was removed to yield pure product 0.340 g 80%). Previously characterized.[16]

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.27 – 6.23 (m, 2H), 5.48 – 5.41 (m, 2H), 2.17 (q, *J* = 7.2, 4H), 1.42 – 1.23 (m, 8H), 0.92 – 0.87 (m, 6H).

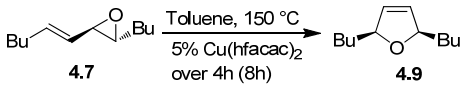


4.36 **4.8**

(Z, cis)-2-Butyl-3-(hex-1-enyl)oxirane (**4.8**): To a 20 mL round bottom flask with a magnetic stir bar was added 0.200 g (1.2 mmol) of (Z,Z)-dodeca-5,7-diene and 4 ml of acetone. The reaction was cooled to 0^{o}C and 15 mL of dimethyldioxirane[3] (1.2 equiv., ~0.1 M in acetone) was added in 5 mL portions. Reaction was monitored by TLC (2.5% Et_2O : 97.5% pentane, $KMnO_4$) until complete and then solvent was evaporated

and the product was purified by silica gel chromatography (2.5% Et_2O : 97.5% pentane) to yield 193 mg (1.06 mmol, 88%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.76 (dtd, *J* = 11.1, 7.6, 0.9, 1H), 5.21 (ddt, *J* = 11.4, 8.4, 1.5, 1H), 3.64 (ddd, *J* = 8.4, 4.3, 1.0, 1H), 3.07 (ddd, *J* = 6.3, 5.7, 4.4, 1H), 2.31 – 2.13 (m, 2H), 1.64 – 1.54 (m, 2H), 1.54 – 1.44 (m, 3H), 1.44 – 1.30 (m, 9H), 0.91 (t, *J* = 7.1, 6H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 137.4, 123.8, 58.6, 52.8, 31.7, 28.5, 28.0, 27.5, 22.5, 22.3, 14.0, 13.9. **IR** (neat) 2954, 2862, 1558, 1521, 1311, 1150, 1062, 955 cm^{-1}. **HRMS** (EI^+) m/z 182.1669 [calculated mass for $C_{12}H_{22}O$ (M^+) 182.1671].



4.7 **4.9**

cis-2,5-Dibutyl-2,5-dihydrofuran (**4.9**): To a flame dried 13x100 mm threaded culture tube was added 24 mg of substrate (**4.7**) (0.13 mmol) in 1 mL of dry toluene. The culture tube was fitted with a threaded septum cap and then submerged in an oil bath at 150ºC. A syringe pump was used to add 0.5 mL of toluene over 4 hours (1.25 mol%/hour) which contained 3.3 mg of $Cu(hfacac)_2$ (0.0066 mmol, 0.05 equiv.). The solution was heated for a total of 8 hours and then cooled to room temperature. The reaction mixture was filtered through neutral alumina (activity grade 1) washing with EtOAc and then purified by flash chromatography on silica gel (5% ether : 95% pentane, $KMnO_4$) to yield 19.0 mg (79%, 0.10 mmol). (Crude diastereomeric ratio 15:1, purified >20:1 cis:trans).

^{1}H NMR (500 MHz, C_6D_6) δ 5.54 (d, *J* = 0.6, 2H), 4.86 – 4.70 (m, 2H), 1.69-0.99 (m, 12H), 0.86 (t, *J* = 7.3, 6H). **^{13}C NMR** (125 MHz, C_6D_6) δ 130.9, 86.3, 37.7, 28.6, 23.5, 14.7. **IR** (neat) 2957, 2927, 2859, 1749, 1717, 1684, 1672, 1522, 1458, 1321 cm^{-1}. **HRMS** (EI^+) *m/z* 182.1671 [calculated mass for $C_{12}H_{22}O$ (M^+) 182.1671].

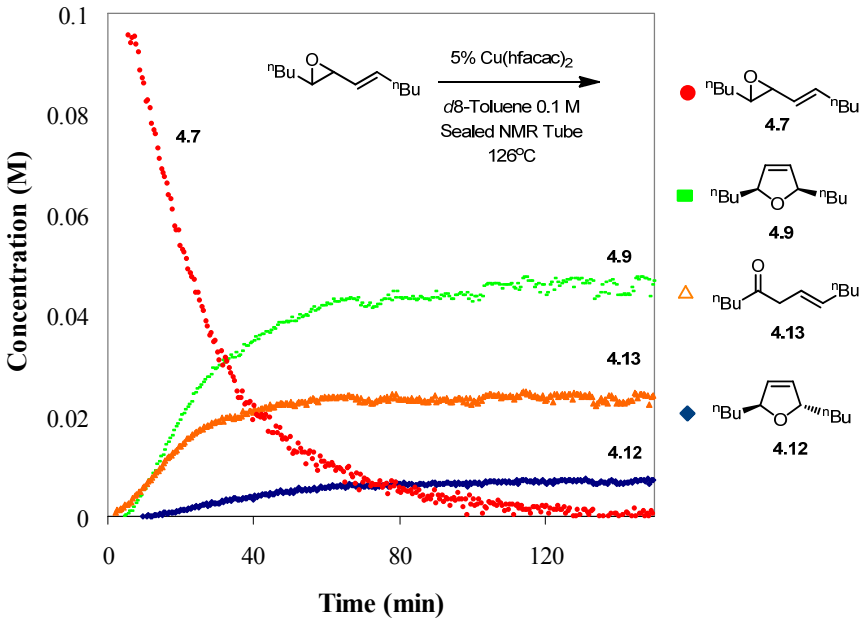
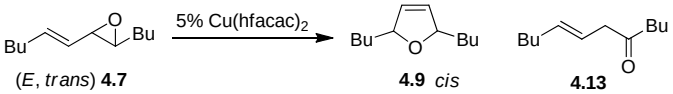


Figure A4.1: NMR Experiment of **4.7**

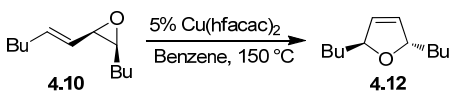
Table A4.1: Solvent-Temperature Relationships for Three Different Non-Polar Solvents



(*E*, *trans*) **4.7** **4.9** *cis* **4.12** *trans* **4.13**

Entry [a]	Solvent	Temperature (°C)	Chemoselectivity (**4.9**+**4.12**:**4.13**)	Pressure [b] (psi)
1	Toluene	150	3 : 1	17
2	Toluene	125	1 : 4	10
3	Toluene	100	1 : >20	3
5	Benzene	125	6 : 1	27
6	Benzene	100	1.5 : 1	17
7	Benzene	75	1 : >20	8
9	Xylene	225	3 : 1	45
10	Xylene	150	1 : 1	10
11	Xylene	100	1 : 5	5

Conditions: 5 mol% $Cu(hfacac)_2$, 0.15M and 15 hours. a) All reactions were run to full conversion, b) These numbers were obtained by directly attaching a pressure gauge to the vessel.



4.10 **4.12**

trans-2,5-Dibutyl-2,5-dihydrofuran (**4.12**): To a flame dried 13 x 100 mm culture tube was added 3.4 mg of $Cu(hfacac)_2$ (0.0069 mmol, 0.05 equiv). To this vial was added 25 mg of vinyloxirane (**4.10**) (0.14 mmol) dissolved in 1.1 ml (0.125 M) benzene. The tube was sealed and reinforced with Teflon tape. The solution was submersed in an oil bath at 150ºC for 3 hours and then cooled to room temperature. The solution was filtered through neutral alumina (activity grade 1) washing with EtOAc. The solvent was removed *in vacuo* and flash chromatography (5% ether : 95% pentane, $KMnO_4$) with silica was performed to yield 16.6 mg (66%, 0.91 mmol). (Crude diastereomeric ratio 1:18, purified >1:20 cis:trans).

^{1}H NMR (500 MHz, C_6D_6) δ 5.53 (s, 2H), 4.88 – 4.78 (m, 2H), 1.72 – 1.03 (m, 12H), 0.87 (t, *J* = 7.3, 6H). **^{13}C NMR** (125 MHz, C_6D_6) δ 130.7, 86.1, 36.9, 28.4, 23.6, 14.7. **IR** (neat) 2957, 2929, 2859, 2360, 2341, 1458, 1377, 1108, 1079 cm^{-1}. **HRMS** (EI^+) *m/z* 182.1671 [calculated mass for $C_{12}H_{22}O$ (M^+) 182.1671].

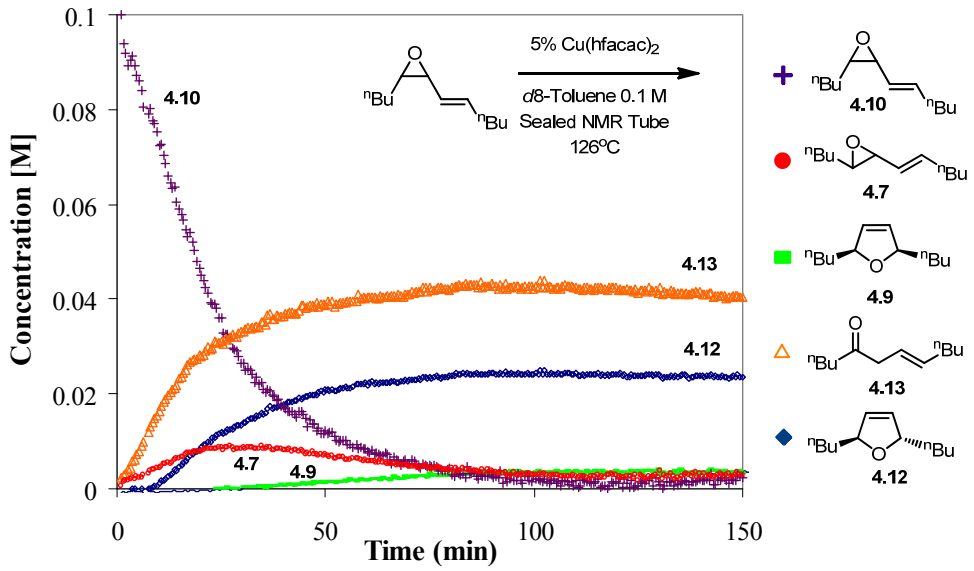
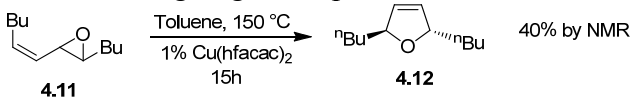
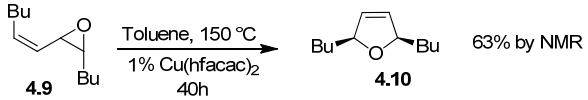


Figure A.4.2: NMR Experiment of **4.10**

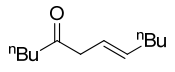
Rearrangement of **4.11** according to general procedure.



Rearrangement of **4.9** according to general procedure.

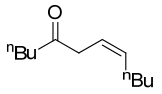


Rearrangements of **4.7, 4.10, 4.8, 4.11** produce **4.9**, **4.37**, and **4.38** as byproducts. They are observable in NMR tube experiments or observable in the crude NMR prior to removal of $Cu(hfacac)_2$. Compound **4.13**[77] and **4.38**[8] are isolable and spectral data matches existing information. Compound **4.37**[9] was not isolable but assumed by it's similarity to **4.13**.



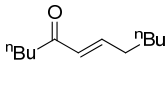
4.13

(E)-Dodec-7-en-5-one (4.13)



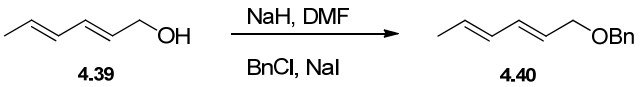
4.36

(Z)-Dodec-7-en-5-one (4.37)



4.38

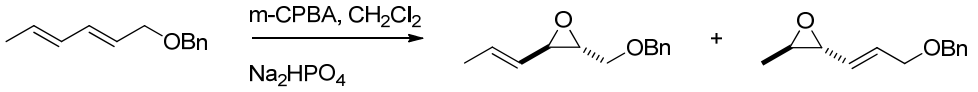
(E)-Dodec-6-en-5-one (4.38)



4.39 **4.40**

(E,E)-1-Benzyloxy-2,4-hexadiene: A 1L flask equipped with a stir bar containing DMF (500 mL) and sodium hydride (60% dispersion in mineral oil, 4.49 g, 112.24 mmol) was cooled to 0°C in an ice bath, and then a solution of (2*E*, 4*E*)-2,4-hexadien-1-ol (10.0 g, 102 mmol) in DMF was slowly added. After 1 hour, sodium iodide (0.49 g, 20.5 mmol) and benzyl chloride (11.8 mL, 13.0 g, 102 mmol) were added. After 2 hours, the reaction was quenched with water and diluted with diethyl ether. The layers were separated, and the aqueous layer was extracted (2x) with diethyl ether. The combined organic portions were then washed with brine, dried over $MgSO_4$, and the solvent was removed *in vacuo*. The crude product was purified by chromatography to give the product as colorless oil (16.26 g, 85%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.26 (m, 5H), 6.23 (dd, *J* = 15.2, 10.5, 1H), 6.13 – 6.03 (m, 1H), 5.71 – 5.60 (m, 2H), 4.51 (s, 2H), 4.05 (d, *J* = 6.3, 2H), 1.77 (d, *J* = 6.7, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.6, 133.6, 131.0 130.3, 128.6, 128.0, 127.8, 126.8, 72.1, 70.8, 18.3. **IR** (neat) 3062, 3026, 2932, 2910, 2853, 1496, 1453, 1361, 1113, 1073, 990 cm^{-1}. **HRMS** (EI^+) *m/z* 188.1198 [calculated mass for $C_{13}H_{16}O$ (M^+) 188.1201].



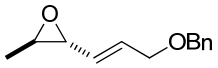
4.40 **4.14b** **4.14a**

2-((E)-3-(Benzyloxy)prop-1-en-1-yl)-3-methyloxirane (**4.14a**) *and 2-((benzyloxy)methyl)-3-((E)-prop-1-en-1-yl)oxirane* (**4.14b**): To a 500 mL RBF equipped with a stir bar was added methylene chloride (300 mL), (*E,E*)-1-benzyloxy-2,4-hexadiene (5.9 g, 31.3 mmol), Na_2HPO_4 (7.73 g, equal mass with m-CPBA), and *m*-CPBA (77%, 7.73 g, 34.5 mmol). After 1 hour, the reaction was cooled to 0°C and filtered through celite. It was then diluted with additional diethyl ether and washed

with 1 M NaOH (1x), a saturated $NaHCO_3$ solution (2x), water, and dried over $MgSO_4$. The solvent was removed *in vacuo* to give a clear oil (6.27 g, 98%) that was a 1.5:1 (**4.14a**:**4.14b**) mixture of regioisomers. The regioisomeric vinyl oxiranes could be separated by column chromatography (10-20% Et_2O : 90-80% pentane).

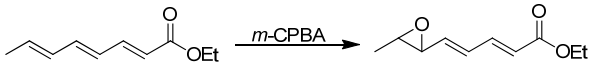
4.14b

2-((Benzyloxy)methyl)-3-((E)-prop-1-en-1-yl)oxirane (**4.14b**): **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.51-7.11 (m, 5H), 6.01 – 5.88 (m, 1H), 5.20 (dddd, *J* = 15.3, 8.3, 3.1, 1.5, 1H), 4.67 – 4.49 (m, 2H), 3.74 (dd, *J* = 11.5, 3.2, 1H), 3.51 (dd, *J* = 11.5, 5.5, 1H), 3.24 (dd, *J* = 8.3, 2.2, 1H), 3.13 – 3.07 (m, 1H), 1.74 (dd, *J* = 6.6, 1.6, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.1, 132.5, 128.6, 128.1, 128.0, 128.0, 73.5, 70.2, 58.8, 56.3, 18.1. **IR** (neat) 3087, 3063, 3029, 2989, 2966, 2938, 2917, 2857, 1496, 1453, 1364, 1239, 1206, 1105, 963, 874, 739, 699 cm^{-1}. **HRMS** (EI^+) *m/z* 204.11496 [calculated mass for $C_{13}H_{16}O_2$ (M^+) 204.11503].



4.14a

2-((E)-3-(Benzyloxy)prop-1-en-1-yl)-3-methyloxirane (**4.14a**) Characterization data matched previously reported in the literature.[10]

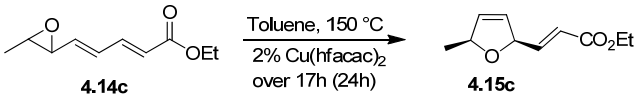


4.41 **4.14c**

(2E,4E)-Ethyl 5-(3-methyloxiran-2-yl)penta-2,4-dienoate (**4.14c**): To a 200 mL flame dried flask with magnetic stir bar was added 120 mL of methylene chloride. To this solution was added 2.00 g of (2E,4E,6E)-ethyl octa-2,4,6-trienoate[11] (12.0 mmol, 1 equiv.). Next, was added 2.7 g of Na_2HPO_4 followed by 2.7 g of m-CPBA (15.6 mmol, 1.3 equiv.). The solution was stirred at room temperature until the starting material was consumed. The solution was cooled to 0°C and then filtered through celite. The organic filtrate was washed 3 times with sat. $NaHCO_3$ and once with H_2O. The solution was dried with Na_2SO_4 and the solvent removed *in vacuo*. The product was purified by silica gel chromatography (15% Et_2O : 85% pentane) to yield 1.73 g of product (79%).

^{1}H NMR (500 MHz, C_6D_6) δ 7.36 (ddd, *J* = 15.4, 11.2, 0.7, 1H), 6.07 (dd, *J* = 15.3, 11.2, 1H), 5.87 (dd, *J* = 15.4, 0.6, 1H), 5.34 (dd, *J* = 15.3, 7.5, 1H), 4.05 (q, *J* = 7.1, 2H), 2.62 (dd, *J* = 7.5, 1.8, 1H), 2.42 (qd, *J* = 5.1, 2.0, 1H), 0.99 (t, *J* = 7.1, 3H), 0.94 (d, *J* = 5.1, 3H). **^{13}C NMR** (126 MHz, C_6D_6) δ 166.8, 143.5, 140.1, 131.1, 122.7, 60.6,

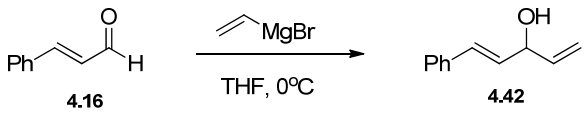
58.4, 57.1, 17.8, 14.7. **IR** (neat) 2984, 2932, 1713, 1644, 1619, 1305, 1231, 1145, 1000, 853 cm^{-1}. **HRMS** (EI^+) *m/z* 182.0941 [calculated mass for $C_{10}H_{14}O_3$ 182.0943]



4.14c **4.15c**

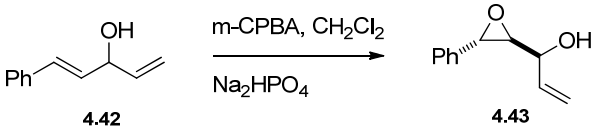
(E)-Ethyl 3-((cis)-5-methyl-2,5-dihydrofuran-2-yl)acrylate (**4.15c**): To a flame dried 13x100 mm threaded culture tube was added 25 mg of substrate (**4.14c**) (0.14 mmol) in 1 mL of dry toluene. The culture tube was fitted with a threaded septum cap and then submerged in an oil bath at 150ºC. A syringe pump was used to add 0.5 mL of toluene over 17 hours (0.12 mol%/hour) which contained 1.4 mg of $Cu(hfacac)_2$ (0.0027 mmol, 0.02 equiv.). The solution was heated for a total of 24 hours and then cooled to room temperature. The reaction mixture was filtered through neutral alumina (activity grade 1) washing with EtOAc and then purified by flash chromatography on silica gel (20% ether : 80% pentane, $KMnO_4$) to yield 21.0 mg (84%, 0.12 mmol). (Crude diastereomeric ratio 8:1, purified >20:1 cis:trans).

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.83 (dd, *J* = 15.6, 5.3, 1H), 5.98 (d, *J* = 15.5, 1H), 5.80 – 5.77 (m, 1H), 5.66 (d, *J* = 6.0, 1H), 5.31 – 5.22 (m, 1H), 4.98 – 4.89 (m, 1H), 4.13 (q, *J* = 7.2, 2H), 1.25 (d, *J* = 6.4, 3H), 1.22 (t, *J* = 7.2, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.7, 147.9, 132.6, 127.1, 120.7, 85.0, 83.1, 60.7, 22.9, 14.5. **IR** neat 2981, 2954, 2873, 1721, 1657, 1596, 1448, 1370, 1303, 1275, 1180, 1039, 981, 841 cm^{-1};. **HRMS** (EI^+) *m/z* 182.09420 [calculated mass for $C_{10}H_{14}O_3$ (M+H) 182.09430].



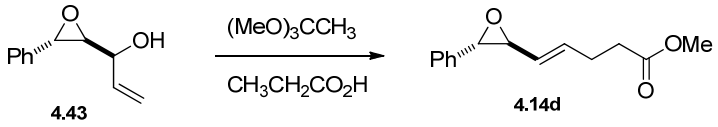
4.16 **4.42**

1-Phenyl-1,4-pentadien-3-ol: To a 1L flask equipped with a stir bar was added THF (300 mL) and *trans*-cinnamaldehyde (8.4 g, 63.6 mmol). The flask was then cooled in an ice bath, and a solution of vinyl magnesium bromide (0.7 M, 100 mL, 70 mmol) was added. After 2 h, the reaction was quenched with water and HCl (1M). The layers were separated, and the aqueous layer was extracted with diethyl ether. The organic portions were combined and dried over $MgSO_4$. The solvent was removed *in vacuo* to leave the product as an orange oil (10.02 g, 99%). The spectral data matched that previously published in the literature.[12]



4.42 **4.43**

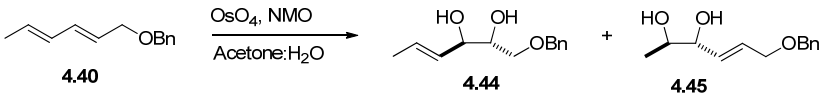
trans-1,2-Epoxy-1-phenyl-4-penten-3-ol: To a 250 mL round bottom flask equipped with a stir bar was cooled in an ice bath. Then methylene chloride (180 mL), 1-phenyl-1,4-pentadien-3-ol (3.00 g, 18.73 mmol), and Na_2HPO_4 (4.85 g, equal mass with m-CPBA) were added. After a few minutes, *m*-CPBA (77%, 4.83, 21.54 mmol) was added, and the reaction was allowed to stir at 0°C. After about 2.5 hours, the reaction was filtered through celite and then washed with NaOH (1 M), sat. $NaHCO_3$, sat. NaCl, and dried over Na_2SO_4 The solvent was removed *in vacuo*, and the product was obtained as a yellow oil (3.06 g, 94%) that did not require further purification and matched previously reported data.[12]



4.43 **4.14d**

Methyl trans-6,7-epoxy-7-phenyl-4-heptenoate (**4.14d**): To a 25 mL RBF equipped with a stir bar was added toluene (8 mL), *trans*-1,2-epoxy-1-phenyl-4-penten-3-ol (1.03 g, 5.8 mmol), trimethyl orthoacetate (3.6 mL, 3.4 g, 28.3 mmol), and propionic acid (0.05 mL, 0.05 g, 0.67 mmol). The reaction was allowed to reflux for 18 hours, and then the toluene was removed *in vacuo* and the crude product was purified by chromatography (5 – 30% Et_2O : 95 – 70% pentane) to give a yellow oil (1.13 g, 83%).

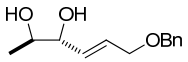
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.19 (m, 5H), 5.98 – 5.85 (m, 1H), 5.35 (dd, *J* = 15.5, 7.8, 1H), 3.71 (d, *J* = 2.0, 1H), 3.65 (s, 3H), 3.28 (dd, *J* = 7.8, 1.8, 1H), 2.40 (d, *J* = 2.7, 4H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.4, 137.3, 134.8, 128.7, 128.4, 128.4, 125.6, 62.9, 60.4, 51.9, 33.5, 27.0. **IR** (neat) 3088, 3064, 3033, 2998, 2951, 2924, 2846, 1737, 1458, 1437, 1363, 1249, 1199, 1170 cm^{-1}. **HRMS** (EI^+) *m/z* 232.1102 [calculated mass for $C_{14}H_{16}O_3$ (M^+) 232.1100].



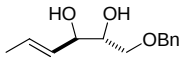
4.40 **4.44** 9% **4.45** 46%

(E)-1-(Benzyloxy)hex-4-ene-2,3-diol (**4.44**) *and (E)-6-(benzyloxy)hex-4-ene-2,3-diol* (**4.45**): To a 250 mL round bottom flask was added 2.00 g of (E,E)-1-benzyloxy-2,4-hexadiene (0.011 mol) followed by 50 mL of acetone and 50 mL of distilled water. Next, 1.4 g of N-methylmorpholine-N-oxide (0.012 mol, 1.1 equiv.) followed by 1.3 mL of 2.5% OsO_4 solution in ^{t}BuOH (0.10 mmol, 0.01 equiv.) This solution was stirred vigorously at room temperature for 14 hours. The reaction was cooled to 0^{o}C and quenched with a solution of sodium bisulfite and diluted with ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3x).

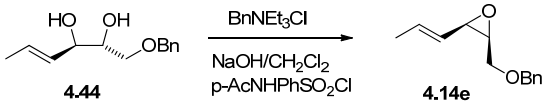
The organic portions were combined and dried over Na_2SO_4. The solvent was removed *in vacuo* and the product was purified by chromatography (80% ether : 20% pentane, anisaldehyde) to yield (E)-6-(benzyloxy)hex-4-ene-2,3-diol 1.08 g (46%, 4.9 mmol); (E)-1-(benzyloxy)hex-4-ene-2,3-diol 0.20 g (9%, 0.91 mmol), starting material 0.21 g (11 %, 1.1 mmol).



(E)-6-(Benzyloxy)hex-4-ene-2,3-diol (**4.45**): **^{1}H NMR** (300 MHz, $CDCl_3$) δ 7.42 – 7.21 (m, 5H), 6.01 – 5.86 (m, 1H), 5.81 – 5.63 (m, 1H), 4.52 (s, 2H), 4.04 (d, *J* = 5.5, 2H), 3.86 (dd, *J* = 10.6, 6.5, 1H), 3.70 – 3.57 (m, 1H), 2.53 (dd, *J* = 6.9, 4.0, 2H), 1.17 (d, *J* = 6.3, 3H); **^{13}C NMR** (75 MHz, $CDCl_3$) δ 138.2, 132.1, 123.0, 128.6, 128.0, 127.9, 77.1, 72.6, 70.8, 70.2, 19.1. **IR** (neat) 3387, 2971, 2860, 1453, 1362, 1264, 1101, 1075, 1026, 972, 737, 697 cm^{-1}.



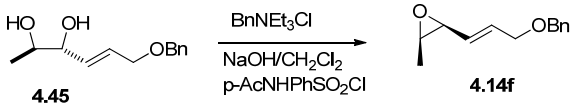
(E)-1-(Benzyloxy)hex-4-ene-2,3-diol (**4.44**): **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.39 – 7.23 (m, 5H), 5.77 – 5.64 (m, 1H), 5.45 (ddd, *J* = 15.3, 7.2, 1.6, 1H), 4.55 (d, *J* = 11.9, 1H), 4.49 (d, *J* = 11.9, 1H), 4.04 (t, *J* = 6.6, 1H), 3.67 – 3.59 (m, 1H), 3.56 (dd, *J* = 9.8, 3.5, 1H), 3.47 (dd, *J* = 9.8, 6.0, 1H), 3.13 (bs, 1H), 3.02 (bs, 1H), 1.71 – 1.64 (m, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.8, 129.9, 129.5, 128.5, 128.1, 127.9, 73.6, 73.5, 73.4, 71.5, 18.0; **IR** (neat) 3443, 2931, 2856, 1671, 1605, 1451, 1206, 1116, 966, 734, 696 cm^{-1}. **HRMS** (CI+) *m/z* 221.11736 [calculated mass for $C_{13}H_{17}O_3$ (M-H) 221.11778].



(E)-2-((Benzyloxy)methyl)-3-(prop-1-en-1-yl)oxirane (**4.14e**): Method adapted from known protocol.[13] To a 25 mL round bottom flask was added 0.25 g of benzyltriethylammonium chloride (1.1 mmol, 1.2 equiv.) followed by 6 mL of dichloromethane and 6 mL of 25% NaOH(aq). The solution was cooled to 0°C and then 0.202 g of (E)-1-(benzyloxy)hex-4-ene-2,3-diol (0.91 mmol) was added. Lastly, 0.250 g of 4-acetamidobenzenesulfonyl chloride (1.1 mmol, 1.2 eqiuv.) was added and the solution was warmed to room temperature slowly over 1 hour and stirred vigorously at room temperature overnight. The solution was diluted with water and extracted with CH_2Cl_2 twice. The solution was dried on Na_2SO_4 and the solvent removed in vacuo. Flash chromatography (10% ether : 90% pentane, anisaldehyde) with silica was performed to yield 0.108 g (0.53 mmol, 58%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.28 (m, 5H), 5.96 (dq, *J* = 15.3, 6.6, 1H), 5.26 (ddq, *J* = 15.4, 8.0, 1.7, 1H), 4.64 (d, *J* = 11.9, 1H), 4.54 (d, *J* = 11.9, 1H), 3.69 (dd, *J*

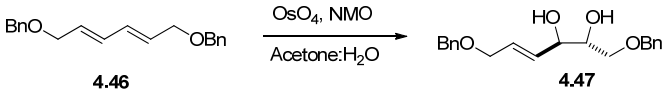
= 11.2, 4.4, 1H), 3.58 (dd, *J* = 11.2, 6.3, 1H), 3.45 (dd, *J* = 8.0, 4.4, 1H), 3.33 (dt, *J* = 6.3, 4.4, 1H), 1.74 (dd, *J* = 6.6, 1.7, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.0, 133.5, 128.6, 128.0, 127.9, 124.8, 73.3, 68.3, 57.0, 56.3, 18.2. **IR** (neat) 2938, 2858, 1453, 1308, 1092, 962, 842, 736, 694 cm^{-1}. **HRMS** (CI+) *m/z* 205.12268 [calculated mass for $C_{13}H_{17}O_2$ (M+H) 205.12286].



4.45 **4.14f**

(E)-2-(3-(Benzyloxy)prop-1-en-1-yl)-3-methyl-cis-oxirane (**4.14f**): Method adapted from known protocol.[13] To a 13 x 100 mm culture tube was added 0.050 g of benzyltriethylammonium chloride (0.22 mmol, 1.9 equiv.) followed by 1 mL of dichloromethane and 1 mL of 25% NaOH(aq). The solution was cooled to 0°C and then 0.050 g of (E)-6-(benzyloxy)hex-4-ene-2,3-diol (0.11 mmol) was added. Lastly, 31.6 mg of 4-acetamidobenzenesulfonyl chloride (0.14 mmol, 1.2 eqiuv.) was added and the solution was warmed to room temperature slowly over 1 hour and stirred vigorously at room temperature overnight. The solution was diluted with water and extracted with CH_2Cl_2 twice. The solution was dried on Na_2SO_4 and the solvent removed in vacuo. Flash chromatography (10% ether : 90% pentane, anisaldehyde) with silica was performed to yield: 0.012 g (0.059 mmol, 52%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 5H), 6.05 (ddd, *J*=15.6, 6.0, 5.3, 1H), 5.70 – 5.58 (m, 1H), 4.54 (s, 2H), 4.08 (dd, *J*=5.6, 1.0, 2H), 3.43 (dd, *J*=7.7, 4.2, 1H), 3.28 – 3.17 (m, 1H), 1.30 (dd, *J*=5.5, 0.7, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.3, 133.3, 128.6, 128.0, 127.9, 127.2, 72.5, 70.1, 56.8, 54.8, 13.6. **IR** (neat) 2914, 2849, 1451, 1276, 1057, 966, 738 cm^{-1}. **HRMS** (CI+) *m/z* 205.12314 [calculated mass for $C_{13}H_{17}O_2$ (M+H) 205.12286].

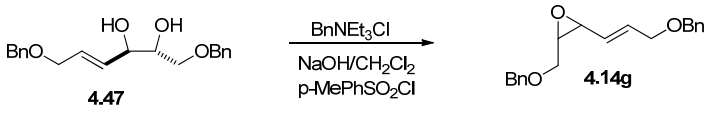


4.46 **4.47**

1,6-bis(Benzyloxy)hex-4-ene-2,3-diol (**4.45**): To a 100 mL round bottom flask was added 1.67g of (2E,4E)-1,6-bis(benzyloxy)hexa-2,4-diene (5.68 mmol) followed by 25 mL of acetone and 25 mL of distilled water. The solution was cooled to 0°C then 0.732 g of N-methylmorpholine-N-oxide (6.25 mmol, 1.1 equiv.) followed by 0.7 mL of 2.5% OsO_4 solution in ^{t}BuOH (0.057 mmol, 0.01 equiv.) This solution was stirred vigorously at room temperature for 14 hours. The reaction was cooled to 0°C and quenched with a solution of sodium bisulfite and diluted with ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3x). The organic portions were combined and dried over Na_2SO_4. The solvent was removed *in vacuo* and the product was purified by chromatography (70% ether : 30% pentane,

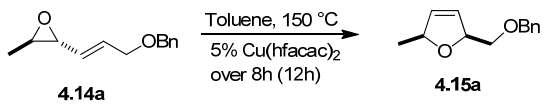
anisaldehyde) to yield 1,6-bis(benzyloxy)hex-4-ene-2,3-diol 0.913g (49%, 2.7 mmol); staring material 0.45 g (27%, 1.5 mmol).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 – 7.16 (m, 10H), 5.95 – 5.82 (m, 1H), 5.76 (dd, *J* = 15.6, 6.1, 1H), 4.57 (d, *J* = 11.9, 1H), 4.50 (s, 2H), 4.50 (d, *J* = 2.6, 1H), 4.19 (t, *J* = 5.5, 1H), 4.02 (d, *J* = 5.4, 2H), 3.68 (dd, *J* = 8.8, 5.1, 1H), 3.61 (dd, *J* = 9.7, 3.6, 1H), 3.53 (dd, *J* = 9.7, 5.7, 1H), 2.76 (s, 2H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 138.3, 137.8, 131.6, 129.8, 128.7, 128.6, 128.1, 128.0, 127.9, 127.8, 73.8, 73.1, 72.9, 72.5, 71.6, 70.1. **IR** (neat) 3415, 2906, 2860, 1496, 1453, 1362, 1206, 1102, 1027, 974 738, 698 cm^{-1}.



(E)-2-((Benzyloxy)methyl)-3-(3-(benzyloxy)prop-1-en-1-yl)oxirane (**4.14g**): Method adapted from known protocol.[13] To a 100 mL round bottom flask was added 3.8 g of benzyltriethylammonium chloride (16.7 mmol, 7.2 equiv.) followed by 24 mL of dichloromethane and 24 mL of 25% NaOH(aq). The solution was cooled to 0^{o}C and then 0.76 g of 1,6-bis(benzyloxy)hex-4-ene-2,3-diol (2.3 mmol) was added. Lastly, 0.44 g of p-Toluenesulfonyl chloride (2.3 mmol, 1.0 eqiuv.) was added and the solution was warmed to room temperature slowly over 1 hour and stirred vigorously at room temperature overnight. The solution was diluted with water and extracted with CH_2Cl_2 twice. The solution was dried on Na_2SO_4 and the solvent removed in vacuo. Flash chromatography (20% ether : 80% pentane, anisaldehyde) with silica was performed to yield 0.483 g (1.6 mmol, 67%).

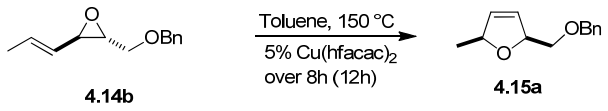
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.13 (m, 10H), 6.00 (dtd, *J* = 15.6, 5.4, 0.8, 1H), 5.56 (ddt, *J* = 15.6, 7.5, 1.6, 1H), 4.58 (d, *J* = 12.0, 1H), 4.49 (d, *J* = 12.0, 1H), 4.47 (s, 2H), 3.98 (dd, *J* = 5.5, 1.6, 2H), 3.65 (dd, *J* = 11.2, 4.3, 1H), 3.53 (dd, *J* = 11.2, 6.3, 1H), 3.45 (ddd, *J* = 7.5, 4.4, 0.7, 1H), 3.31 (dt, *J* = 6.3, 4.4, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.0, 137.8, 133.4, 128.4, 127.7, 127.7, 126.0, 73.1, 72.2, 69.6, 68.0, 56.8, 55.4. **IR** (neat) 3031, 2855, 1698, 1507, 1373, 1091, 965, 736, 696 cm^{-1}. **HRMS** (EI^+) *m/z* 310.15685 [calculated mass for $C_{20}H_{22}O_3$ (M^+) 310.15690].



cis-2-Benzyloxymethyl-5-methyl-2,5-dihydrofuran (**4.15a**): To a flame dried 13x100 mm threaded culture tube was added 25 mg of substrate (**4.14a**) (0.12 mmol) in 1 mL of dry toluene. The culture tube was fitted with a threaded septum cap and then submerged in an oil bath at 150ºC. A syringe pump was used to add 0.5 mL of toluene over 8 hours (0.63 mol%/hour) which contained 3.0 mg of $Cu(hfacac)_2$ (0.0061 mmol,

0.05 equiv.). The solution was heated for a total of 12 hours and then cooled to room temperature. The reaction mixture was filtered through neutral alumina (activity grade 1) washing with EtOAc and then purified by flash chromatography on silica gel (10% ether : 90% pentane, $KMnO_4$) to yield 23.5 mg (94%, 0.12 mmol). (Crude diastereomeric ratio >20:1, purified >20:1 cis:trans).

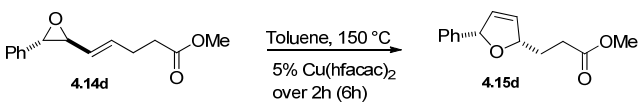
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.00 (m, 5H), 5.85 (d, *J* = 6.0, 1H), 5.78 (d, *J* = 6.0, 1H), 4.99 – 4.90 (m, 2H), 4.66 – 4.54 (m, 2H), 3.54 – 3.47 (m, 2H), 1.29 (d, *J* = 6.3, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.5, 133.1, 128.5, 127.8, 127.7, 127.1, 85.5, 82.5, 74.1, 73.6, 23.0. **IR** (neat) 3312, 3089, 3064, 3031, 2971, 2924, 2859, 1453, 1366, 1094 cm^{-1}. **HRMS** (EI$^+$) *m/z* 202.0996 [calculated mass for $C_{13}H_{14}O_2$ (M-H_2) 202.0994].



4.14b **4.15a**

cis-2-Benzyloxymethyl-5-methyl-2,5-dihydrofuran (**4.15a**): To a flame dried 13x100 mm threaded culture tube was added 25 mg of substrate (**4.14b**) (0.12 mmol) in 1 mL of dry toluene. The culture tube was fitted with a threaded septum cap and then submerged in an oil bath at 150ºC. A syringe pump was used to add 0.5 mL of toluene over 8 hours (0.63 mol%/hour) which contained 3.0 mg of $Cu(hfacac)_2$ (0.0061 mmol, 0.05 equiv.). The solution was heated for a total of 12 hours and then cooled to room temperature. The reaction mixture was filtered through neutral alumina (activity grade 1) washing with EtOAc and then purified by flash chromatography on silica gel (10% ether : 90% pentane, $KMnO_4$) to yield 22.0 mg (88%, 0.11 mmol). (Crude diastereomeric ratio 13:1, purified >20:1 cis:trans).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.00 (m, 5H), 5.85 (d, *J* = 6.0, 1H), 5.78 (d, *J* = 6.0, 1H), 4.99 – 4.90 (m, 2H), 4.66 – 4.54 (m, 2H), 3.54 – 3.47 (m, 2H), 1.29 (d, *J* = 6.3, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.5, 133.1, 128.5, 127.8, 127.7, 127.1, 85.5, 82.5, 74.1, 73.6, 23.0. **IR** (neat) 3312, 3089, 3064, 3031, 2971, 2924, 2859, 1453, 1366, 1094 cm^{-1}. **HRMS** (EI$^+$) *m/z* 202.0996 [calculated mass for $C_{13}H_{14}O_2$ (M-H_2) 202.0994].

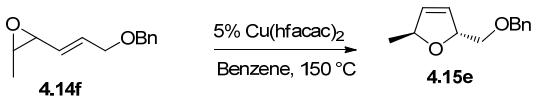


4.14d **4.15d**

Methyl 3-(cis-5-Phenyl-2,5-dihydrofuranyl)-propanoate (**4.15d**): To a flame dried 13x100 mm threaded culture tube was added 25 mg of substrate (**4.14d**) (0.11 mmol) in 1 mL of dry toluene. The culture tube was fitted with a threaded septum cap and then submerged in an oil bath at 150ºC. A syringe pump was used to add 0.5 mL of toluene over 2 hours (0.12 mol%/hour) which contained 2.7 mg of $Cu(hfacac)_2$

(0.0054 mmol, 0.05 equiv.). The solution was heated for a total of 6 hours and then cooled to room temperature. The reaction mixture was filtered through neutral alumina (activity grade 1) washing with EtOAc and then purified by flash chromatography on silica gel (20% ether : 80% pentane, $KMnO_4$) to yield 17.5 mg (70%, 0.075 mmol). (Crude diastereomeric ratio 8:1, purified >20:1 cis:trans).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.39 – 7.27 (m, 5H), 5.94 – 5.88 (m, 2H), 5.76 (d, *J* = 3.8, 1H), 4.98 – 4.90 (m, 1H), 3.65 (s, 3H), 2.56 – 2.37 (m, 2H), 2.11 – 2.02 (m, 1H), 2.00 – 1.88 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 174.2, 141.7, 131.0, 130.2, 128.7, 128.1, 126.9, 87.9, 85.4, 51.8, 31.6, 30.3. **IR** (neat) 3083, 3063, 3030, 2951, 2844, 2930, 2844, 1738, 1493, 1438, 1357, 1252, 1199, 1168, 1065 cm^{-1}. **HRMS** (EI$^+$) *m/z* 232.1100 [calculated mass for $C_{14}H_{16}O_3$ (M^+) 232.1100].

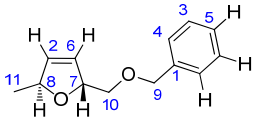


4.14f **4.15e**

2-((Benzyloxy)methyl)-5-methyl-2,5-dihydrofuran (**4.15e**): To a flame dried 13 x 100 mm culture tube was added 3.0 mg of $Cu(hfacac)_2$ (0.0061 mmol, 0.05 equiv). To this vial was added 25 mg of vinyloxirane (**4.14f**) (0.12 mmol) dissolved in 0.8 ml of benzene. The tube was sealed and reinforced with Teflon tape. The solution was submersed in an oil bath at 150ºC for 2 hours and then cooled to room temperature. The solution was filtered through neutral alumina (activity grade 1) washing with EtOAc. The solvent was removed *in vacuo* and flash chromatography (10% ether : 90% pentane, anisaldehyde) with silica was performed to yield 24.0 mg (96%, 0.12 mmol, diastereomeric ratio 1:8 cis:trans).

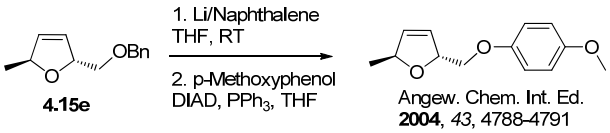
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 5H), 5.88 (dt, *J*=6.0, 1.2, 1H), 5.77 (d, *J*=6.2 1H), 5.07 – 4.98 (m, 2H), 4.62 (d, *J*=12.2, 1H), 4.56 (d, *J*=12.2, 1H), 3.49 (d, *J*=5.3, 2H), 1.27 (d, *J*=6.2, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.5, 133.3, 128.5, 127.9, 127.8, 126.7, 85.0, 82.3, 73.6, 73.1, 21.9. **IR** (neat) 2969, 2958, 1496, 1453, 1094, 1927, 736, 698 cm^{-1}. **LRMS** *m/z* 204 [calculated mass for $C_{13}H_{16}O_2$ (M^+) 204.1150]. Molecular ion too small for high resolution by electron impact, electrospray, and chemical ionization techniques. Structure confirmed by 2D analysis as well as by derivatization to (trans)-2-((4-methoxyphenoxy)methyl)-5-methyl-2,5-dihydrofuran[1414]. This sequence was done by lithium naphthalenide reduction to remove the benzyl group and a mitsunobu reaction using 4-methoxyphenol.

Table A4.2: 2D-NMR analysis of **4.15e**



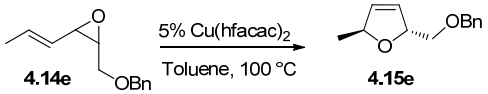
4.15e

	C	H	COSY	HMBC	NOESY
1	138.5	-	-	7.34, 4.62, 4.56	-
2	133.3	5.88	5.03	1.27, 5.77, 5.0	1.27
3	128.5	7.34	7.27	7.34, 7.27	4.62, 4.56
4	127.9	7.34	7.27	7.34, 7.27, 4.62, 4.56	4.62, 4.56
5	127.8	7.27	7.34	7.34	
6	126.7	5.77	5.01	5.88, 5.0, 3.49	3.49
7	85.0	5.03	3.49, 5.01, 5.88	5.88, 5.77, 3.49	
8	82.3	5.01	1.27, 5.03, 5.77	5.88, 5.77, 1.27	
9	73.6	4.56	4.62	7.34, 3.49	7.34, 3.49
		4.62	4.56		7.34, 3.49
10	73.1	3.49	5.03	4.62, 4.56, 5.88	4.62, 4.56, 5.77
11	21.9	1.27	5.01	5.77	5.88, 5.03



4.15e

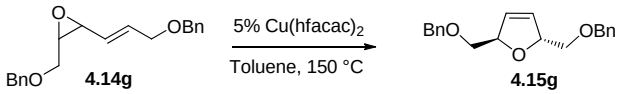
Angew. Chem. Int. Ed. **2004**, *43*, 4788-4791



4.14e **4.15e**

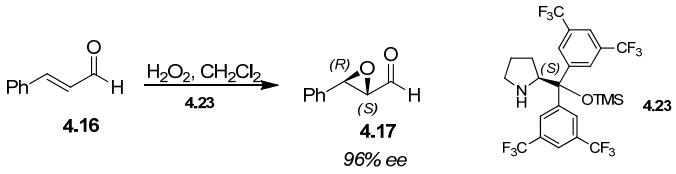
2-((Benzyloxy)methyl)-5-methyl-2,5-dihydrofuran (**4.15e**): To a flame dried 13 x 100 mm culture tube was added 3.0 mg of $Cu(hfacac)_2$ (0.0061 mmol, 0.05 equiv). To this vial was added 24.6 mg of vinyloxirane (**4.14e**) (0.12 mmol) dissolved in 0.8 ml of toluene. The tube was sealed and reinforced with Teflon tape. The solution was submersed in an oil bath at 100ºC for 13 hours and then cooled to room temperature. The solution was filtered through neutral alumina (activity grade 1) washing with EtOAc. The solvent was removed in vacuo and flash chromatography (10% ether : 90% pentane, anisaldehyde) with silica was performed. Yield 22.6 mg (92%, 0.11 mmol, diastereomeric ratio 1:6 cis:trans).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.27 (m, 5H), 5.88 (dt, *J*=6.0, 1.2, 1H), 5.77 (d, *J*=6.2 1H), 5.07 – 4.98 (m, 2H), 4.62 (d, *J*=12.2, 1H), 4.56 (d, *J*=12.2, 1H), 3.49 (d, *J*=5.3, 2H), 1.27 (d, *J*=6.2, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ = 138.5, 133.3, 128.5, 127.9, 127.8, 126.7, 85.0, 82.3, 73.6, 73.1, 21.9. **IR** (neat) 2969, 2958, 1496, 1453, 1094, 1927, 736, 698 cm^{-1}; **LRMS** *m/z* 204 [calculated mass for $C_{13}H_{16}O_2$ (M^+) 204.1150].

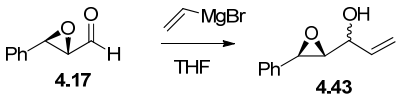


2,5-bis((Benzyloxy)methyl)-2,5-dihydrofuran (**4.15g**): To a flame dried 13 x 100 mm culture tube was added 2.0 mg of $Cu(hfacac)_2$ (0.0040 mmol, 0.05 equiv). To this vial was added 25 mg of vinyloxirane (**4.14g**) (0.081 mmol) dissolved in 0.54 ml of toluene. The tube was sealed and reinforced with Teflon tape. The solution was submersed in an oil bath at 150ºC for 2 hours and then cooled to room temperature. The solution was filtered through neutral alumina (activity grade 1) washing with EtOAc. The solvent was removed *in vacuo* and flash chromatography (20% ether : 80% pentane, anisaldehyde) with silica was performed to yield 23.2 mg (93%, 0.074 mmol, diastereomeric ratio 1:7 cis:trans).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 – 7.18 (m, 10H), 5.92 (bs, 2H), 5.05 (t, *J*=3.4, 2H), 4.58 (d, *J*=3.1, 4H), 3.53 (dd, *J* = 4.8, 3.3, 4H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 138.4, 129.0, 128.5, 127.8, 127.7, 85.7, 73.6, 72.9. **IR** (neat) 3028, 2849, 1603, 1451, 1307, 1202, 1083, 732 cm^{-1}. **HRMS** (EI^+) *m/z* 310.1566 [calculated mass for $C_{20}H_{22}O_3$ (M^+) 310.1569].

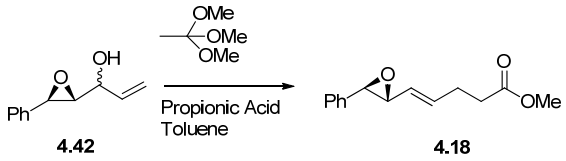


(2S,3R)-3-Phenyloxirane-2-carbaldehyde (**4.17**): Prepared according to published procedure.[15]



1-((2R,3R)-3-Phenyloxiran-2-yl)prop-2-en-1-ol: To a flame dried 250 mL roundbottom flask was added 1.82g of aldehyde **4.17** (12.3 mmol), a magnetic stir bar, and 100 ml of dry THF. The solution was cooled to -78ºC under an atmosphere of N_2. Then 19.5 mL of vinyl magnesium bromide was added (0.7 M in THF (new bottle), 13.7 mmol, 1.1 equiv.) in two portions. The solution was stirred for 1 h at -78ºC and then 2 h at 0ºC The solution was quenched with 20 mL of sat. NH_4Cl and slowly warmed to room temperature. The solution was diluted with distilled water and then extracted with ethyl acetate. The solution was dried on Na_2SO_4 and then the solvent was removed in vacuo. Flash chromatography (30% ether : 70% pentane, anisaldehyde) with silica was performed to yield 1.01 g (47%, 5.7 mmol). The product was a 1.1 : 1 mixture of diastereomers with the (R,R,R)[12] product as the major and was previously known.

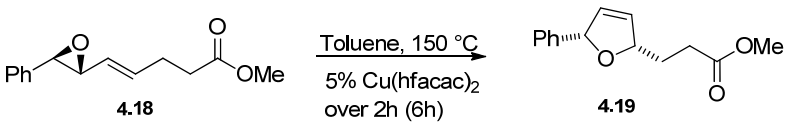
The minor product: **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.26 (m, 5H), 6.05-5.85 (m, 1H), 5.41 (dd, *J* = 3.0, 1.5, 1H), 5.31 – 5.29 (m, 1H), 4.25 (dt, *J* = 8.8, 4.7, 1H), 3.92 (d, *J* = 2.1, 1H), 3.15 (dd, *J* = 4.2, 2.2, 1H), 2.13 (bs, 1H).



4.42 **4.18**

(E)-Methyl 5-((2R,3R)-3-phenyloxiran-2-yl)pent-4-enoate (**4.18**): Prepared identical to compound **4.14d**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.19 (m, 5H), 5.98 – 5.85 (m, 1H), 5.35 (dd, *J* = 15.5, 7.8, 1H), 3.71 (d, *J* = 2.0, 1H), 3.65 (s, 3H), 3.28 (dd, *J* = 7.8, 1.8, 1H), 2.40 (d, *J* = 2.7, 4H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 173.4, 137.3, 134.8, 128.7, 128.4, 128.4, 125.6, 62.9, 60.4, 51.9, 33.5, 27.0. **IR** (neat) 3088, 3064, 3033, 2998, 2951, 2924, 2846, 1737, 1458, 1437, 1363, 1249, 1199, 1170 cm^{-1}. **HRMS** (EI^+) *m/z* 232.1102 [calculated mass for $C_{14}H_{16}O_3$ (M^+) 232.1100]. $[\alpha]_D^{21}$ = + 80.9 (c = 0.045 g/mL, $CHCl_3$).



4.18 **4.19**

Methyl 3-(cis-5-phenyl-2,5-dihydrofuranyl)-propanoate (**4.19**): To a flame dried 13x100 mm threaded culture tube was added 25 mg of substrate (**4.18**) (0.11 mmol) in 1 mL of dry toluene. The culture tube was fitted with a threaded septum cap and then submerged in an oil bath at 150ºC. A syringe pump was used to add 0.5 mL of toluene over 2 hours (0.12 mol%/hour) which contained 2.7 mg of $Cu(hfacac)_2$ (0.0054 mmol, 0.05 equiv.). The solution was heated for a total of 6 hours and then cooled to room temperature. The reaction mixture was filtered through neutral alumina (activity grade 1) washing with EtOAc and then purified by flash chromatography on silica gel (20% ether : 80% pentane, $KMnO_4$) to yield 17.5 mg (70%, 0.075 mmol). (Crude diastereomeric ratio 8:1, purified >20:1 cis:trans)

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.27 (m, 5H), 5.94 – 5.88 (m, 2H), 5.76 (d, *J* = 3.8, 1H), 4.98 – 4.90 (m, 1H), 3.65 (s, 3H), 2.56 – 2.37 (m, 2H), 2.11 – 2.02 (m, 1H), 2.00 – 1.88 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 174.2, 141.7, 131.0, 130.2, 128.7, 128.1, 126.9, 87.9, 85.4, 51.8, 31.6, 30.3. **IR** (neat) 3083, 3063, 3030, 2951, 2844, 2930, 2844, 1738, 1493, 1438, 1357, 1252, 1199, 1168, 1065 cm^{-1}. **HRMS** (EI^+) *m/z* 232.1100 [calculated mass for $C_{14}H_{16}O_3$ (M^+) 232.1100]. **$[\alpha]_D^{21}$** = - 81.6 (c = 0.020 g/mL, $CHCl_3$). Enantiomeric excess determined to be 95% by chiral HPLC.

The analysis of **4.19** was accomplished by eluting with a gradient of 2% ^{i}PrOH: 98% Hexanes going to 5% ^{i}PrOH: 95% hexanes over 30 minutes.

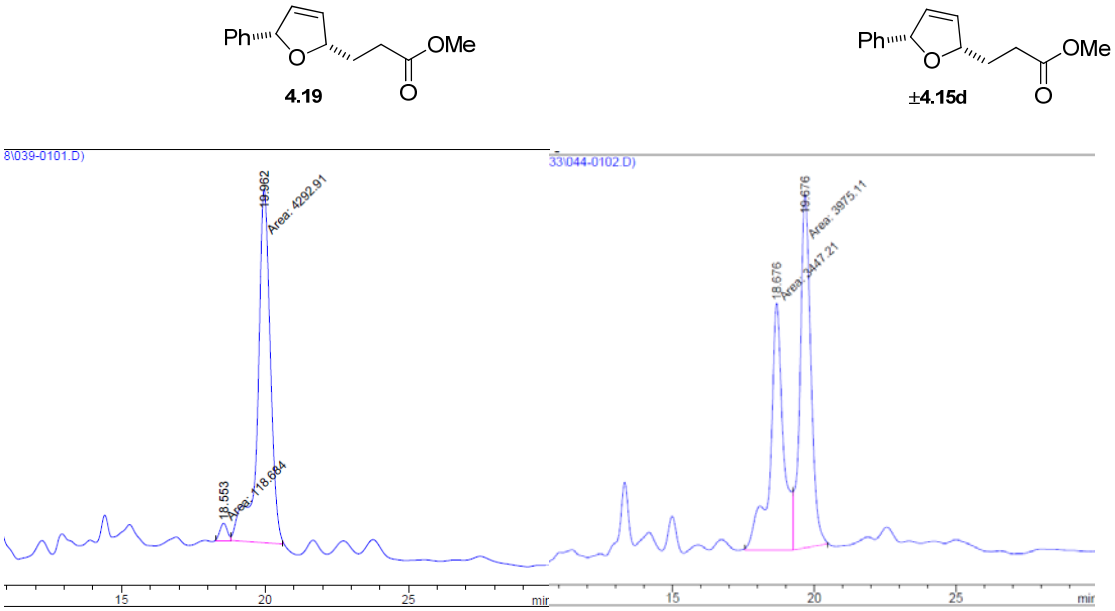
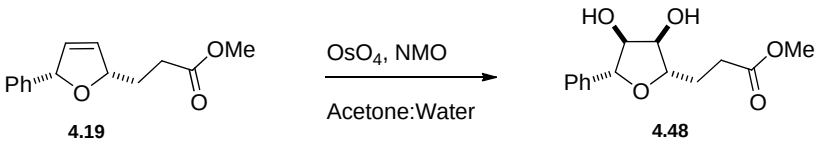
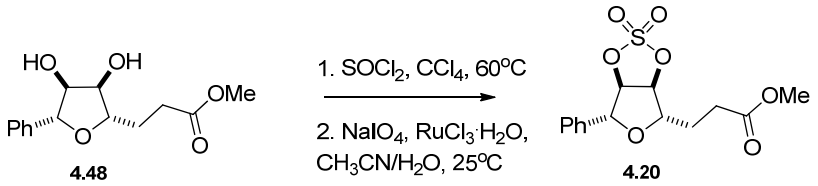


Figure A4.3: HPLC Trace of **4.19** and **±4.15d**



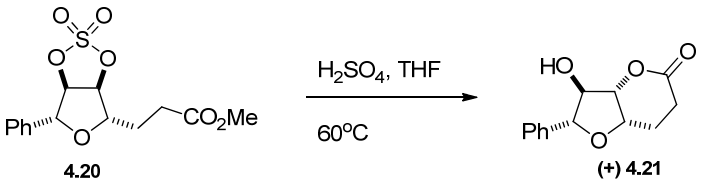
4-epi-Goniothalesdiol: To a stirred flask containing acetone (1 mL), water (1 mL), **4.19** (0.208 g, 0.895 mmol), and 4-methylmorpholine *N*-oxide (0.1865 g, 1.59 mmol, 1.78 equiv.) was added OsO_4 (2.5% *t*BuOH, 0.07 mL). After 15 hours, the reaction was quenched with a solution of sodium bisulfite and diluted with ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3x). The combined organic portions were combined and dried over Na_2SO_4. The solvent was removed *in vacuo* and the product was purified by chromatography (15-75% EtOAc/Hex) to yield 0.237 g (0.89 mmol, 99% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 5H), 4.72 (d, *J* = 5.6, 1H), 3.99 – 3.87 (m, 3H), 3.70 (s, 3H), 2.70 – 2.49 (m, 2H), 2.20 – 2.08 (m, 1H), 2.08 – 1.96 (m, 1H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 174.3, 140.0, 128.7, 128.1, 126.1, 85.0, 82.9, 77.7, 74.9, 52.0, 52.0, 30.6, 28.9.



Cyclic sulfate **4.20:** The cyclic sulfate of **4.48** was made using a literature procedure.[16] To a flame dried 4 mL threaded culture tube was added 47.9 mg of 4-epi-goniothalesdiol (0.18 mmol) and was azeotroped with benzene. To this vial was added 0.3 mL of CCl_4, a stir bar was, and a reflux condenser was attached that was fitted with a drying tube containing $CaCl_2$. The reaction was heated at reflux 25.7 mg (0.216 mmol, 1.2 equiv.) of thionyl chloride was added slowly. The reaction was heated an additional 30 minutes to expel the HCl produced. The solution was then cooled to 0°C followed by addition of 0.22 mL of CH_3CN. Then 57.8 mg (0.27 mmol, 1.5 equiv.) of $NaIO_4$ was added followed by an aqueous solution $RuCl_3{\cdot}H_2O$ (0.1 mg of $RuCl_3{\cdot}H_2O$ [0.003 equiv.] in 0.30 mL of H_2O). The solution was stirred at room temperature for 1 hour and diluted with diethyl ether. The organic layer was washed with water, sat. $NaHCO_3$ solution, and sat. NaCl solution. The organic layer was dried with Na_2SO_4 and the solvent removed. The product can be isolated as a yellow-brown oil after filtration through a plug of silica to yield 51.9 mg (0.16 mmol, 88%).

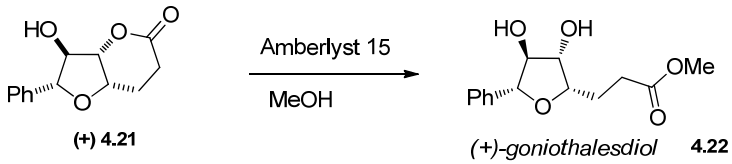
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.30 (m, 5H), 5.04 (d, *J* = 5.8, 1H), 4.97 – 4.91 (m, 2H), 4.26 (dt, *J* = 8.0, 5.4, 1H), 3.70 (s, 3H), 2.66 – 2.48 (m, 2H), 2.33 – 2.20 (m, 1H), 2.18 – 2.11 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ ppm 173.0, 136.2, 129.3, 129.2, 125.9, 86.3, 84.3, 83.5, 81.6, 52.2, 29.9, 27.8;. **$[\alpha]_D^{21}$** = - 1.1 (c = 0.010 g/mL, $CHCl_3$).



Lactone **(4.21):** To a 4 mL vial equipped with a stir bar and containing THF (0.5 mL) was added **4.20** (12.4 mg, 0.038 mmol) followed by a 15% H_2SO_4 aqueous solution (0.25 mL). The vial was then capped and the seal was reinforced with Teflon tape. The vial was heated at 60° C for 14 hours. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate and water, and the layers were separated. The aqueous layer was extracted with ethyl acetate (2x) and the combined organic fractions were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The compound was purified using column chromatography (EtOAc/Hex) and the characterization data was found to match that in the literature[17] to yield 7.7 mg (0.033 mmol, 87%).

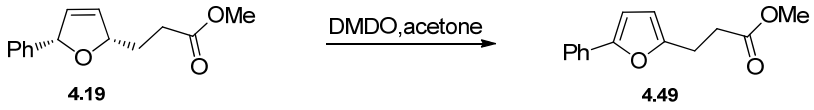
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (m, 5H), 4.82 (dd, *J* = 5.3, 2.4, 1H), 4.65 (d, *J* = 6.6, 1H), 4.49 (dd, *J* = 9.2, 4.4, 1H), 4.25 (dd, *J* = 6.4, 1.9, 1H), 2.73 (m, 1H), 2.51

(td, *J* = 17.1, 5.2, 1H), 2.21 (m, 1H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 171.0, 138.4, 128.9, 128.7, 126.3, 88.3, 85.3, 84.9, 72.5, 26.4, 23.4. $[\alpha]_D$ matched literatue value.[16]



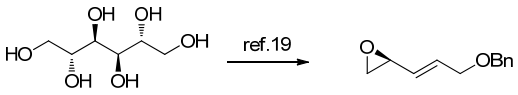
(+)-Goniothalesdiol **4.22**: To a 4 mL threaded culture tube was added 10 mg of lactone **4.21 (**0.043 mmol) and 0.4 mL of dry methanol. Next, 3.5 mg of Amberlyst® 15 (strongly acidic ion exchange resin, sulfonic acid functionality) was added and stirred vigorously with a large stir bar. The reaction was stirred for 10 hours at room temperature followed by quenching with a sat. $NaHCO_3$ solution. The solution was extracted with ethyl acetate three times and then dried with $NaSO_4$. The solvent was removed to yield pure **4.22** to yield 11.3 mg (0.042 mmol, 99%). The product was identical to literature spectra.[18]

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.37 (m, 2H), 7.38 – 7.30 (m, 2H), 7.27 (tt, J = 5.8, 1.3, 1H), 4.59 (d, J = 4.6, 1H), 4.10 – 4.01 (m, 3H), 3.68 (s, 3H), 2.83 (bs, 1H), 2.73 (bs, 1H), 2.61 (dt, J = 16.9, 6.9, 1H), 2.49 (dt, J = 16.9, 7.5, 1H), 2.15 – 1.99 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 174.9, 140.1, 128.7, 128.0, 126.3, 86.2, 85.4, 80.8, 79.1 52.1, 30.8, 23.9. **IR** (neat) 3430, 2925, 1717, 1439, 1262, 1038, 759, 700 cm^{-1}. **$[\alpha]_D^{22}$** +7.2 (c = 0.00167 g/mL, EtOH); Literature[18a] +7.5 (c = 0.23, EtOH).



Methyl 3-(5-phenylfuran-2-yl)propanoate: A solution of DMDO (0.5mL, about 1.5 eq) in acetone was added to dihydrofuran **4.19** (0.0075g, 0.3229 mmol). Upon completion, the solvent was removed *in vacuo*.

^{1}H NMR (400 MHz, C_6D_6) δ ppm 7.63-7.58 (m, 2H), 7.21-6.89 (m, 3H), 6.34 (d, *J* = 3.24, 1H), 5.89 (d, *J* = 3.27, 1H), 3.28 (s, 3H), 2.81 (t, *J* = 7.54, 2H), 2.36 (t, *J* = 7.53, 2H). **HRMS** (EI^+) *m/z* 230.0944 [calculated mass for $C_{14}H_{14}O_3$ (M^+) 230.0943].



D-mannitol (**4.50**) **4.32**

(S,E)-2-(3-(Benzyloxy)prop-1-enyl)oxirane (**4.32**): Compound **4.32** was synthesized in enantiopure form from D-mannitol according to known procedures.[19] Compound matched existing ^{1}H NMR and $[\alpha]_D^{20}$ data.

The analysis of **4.32** was accomplished by eluting with a gradient of 2.5% ^{i}PrOH: 97.5% Hexanes going to 5% ^{i}PrOH: 95% hexanes over 20 minutes.

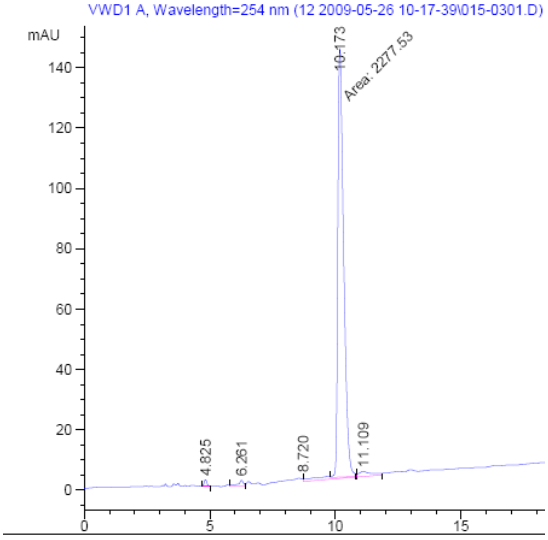
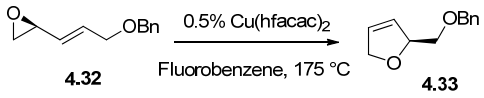


Figure A4.4: HPLC Trace of **4.32**



4.32 **4.33**

(S)-2-(benzyloxymethyl)-2,5-dihydrofuran (**4.33**): To a flame dried 13 x 45 mm culture tube was added 0.16 mg of Cu(hfacac)$_2$ (0.00033 mmol, 0.005 equiv). To this vial was added 12.5 mg of vinyloxirane (4.**32**) (0.066 mmol) dissolved in 0.6 ml fluorobenzene. The tube was sealed and reinforced with Teflon tape. The solution was submersed in an oil bath at 175ºC for 24 hours and then cooled to room temperature. The solution was filtered through neutral alumina (activity grade 1) washing with EtOAc. The solvent was removed in vacuo and flash chromatography (40% ether : 60% pentane, $KMnO_4$) with silica was performed to yield 7.5 mg (60%, 0.039 mmol). Spectral Data matched existing ^{1}H NMR and $[\alpha]_D^{25}$ data.[21]

The analysis of **33** was accomplished by eluting with a gradient of 2.5% ^{i}PrOH: 97.5% hexanes going to 5% ^{i}PrOH: 95% hexanes over 20 minutes. The racemic compound was also made to assess enantioexcess.[21] Product **33** does not racemize with heat or treatment with Cu(hfacac)$_2$.

Racemic Product **33**: Enantioenriched Product **33**:

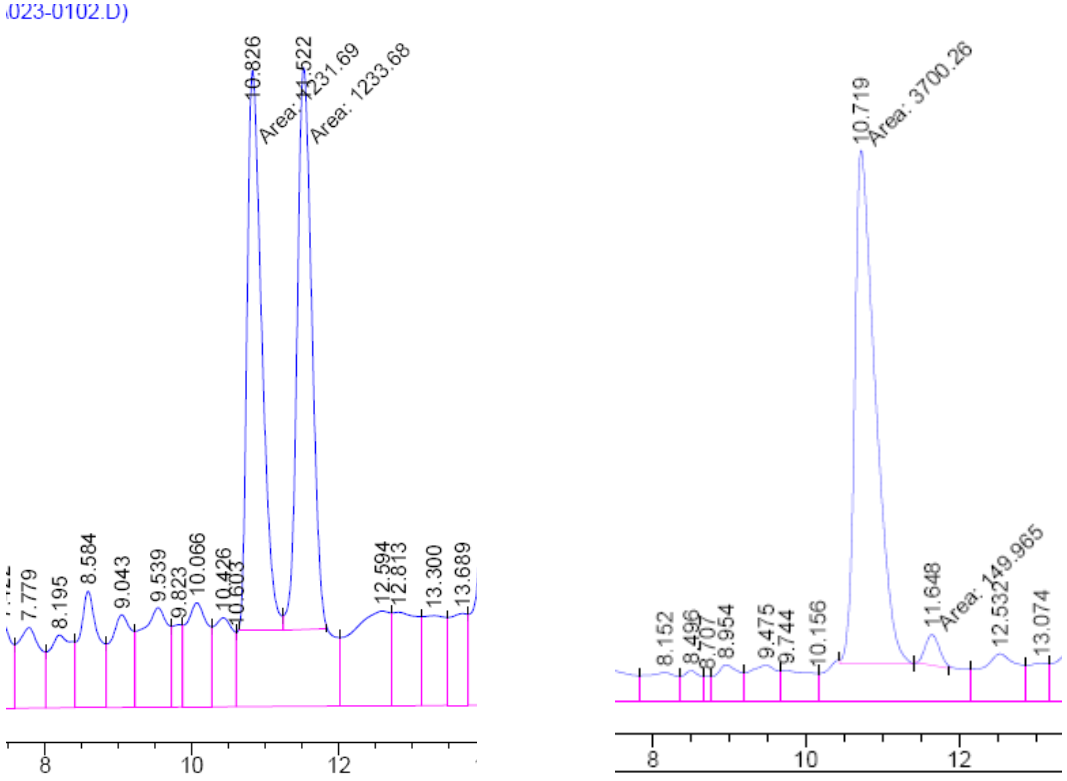
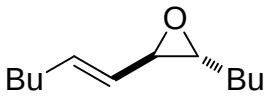
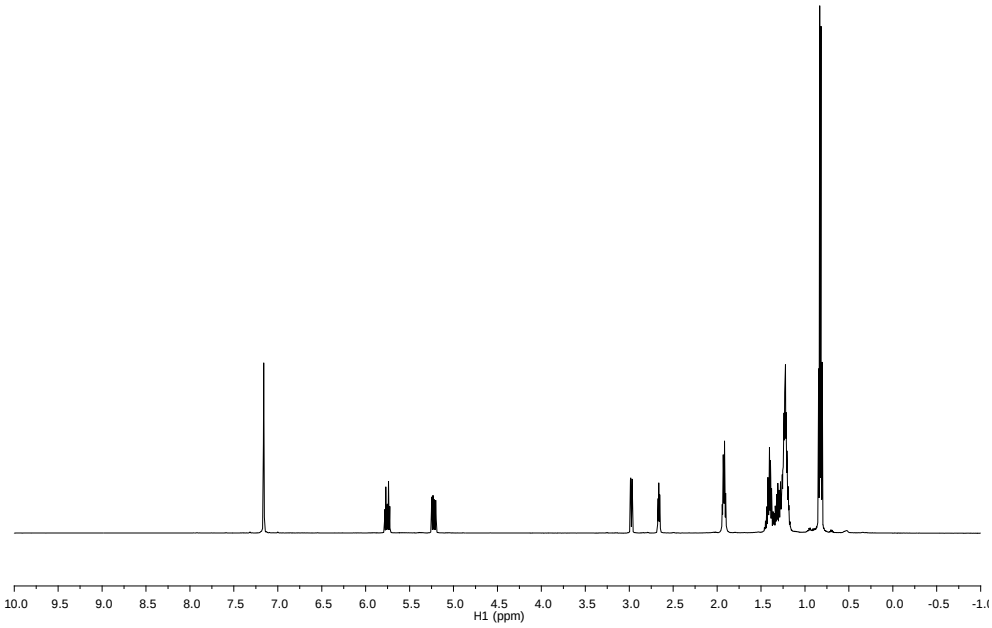


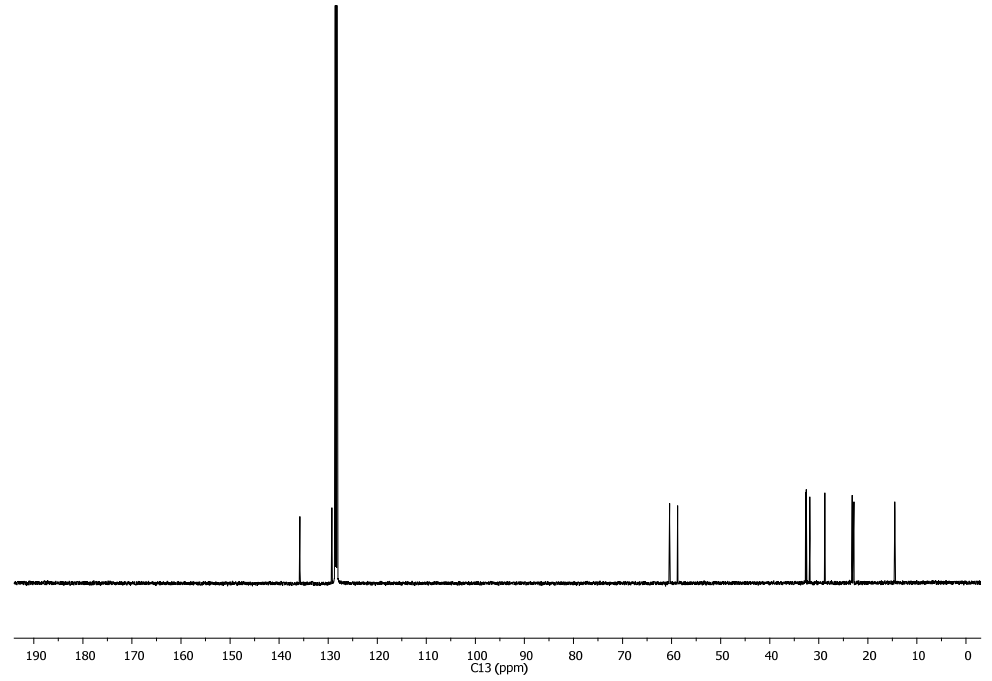
Figure A4.5: HPLC Trace of **4.33**

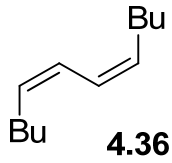
A4.2 ^{1}H and ^{13}C NMR Spectra for Chapter 4



4.7



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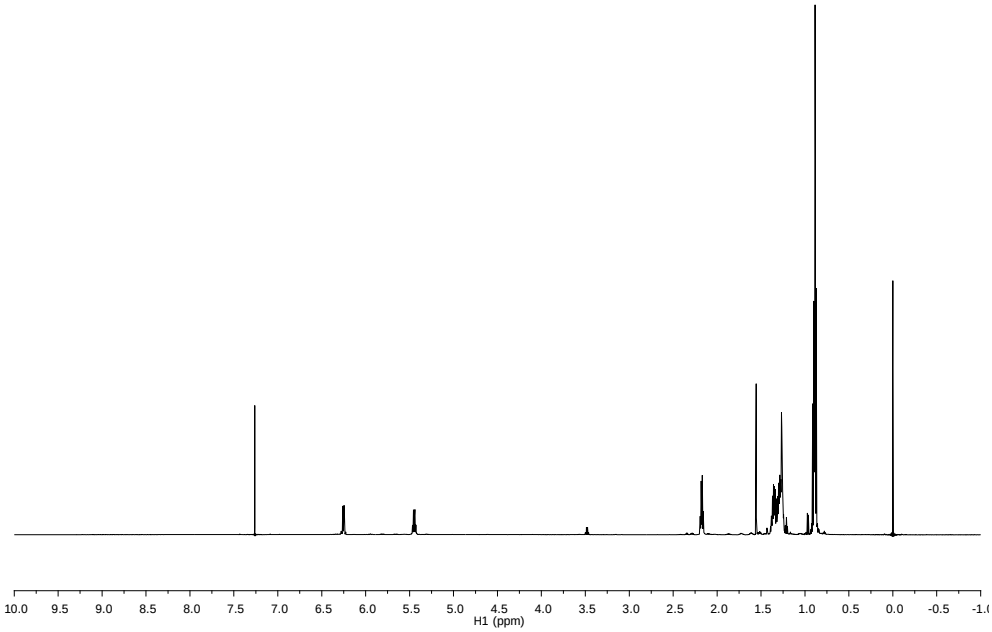
4.36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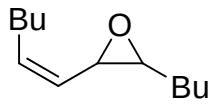
H1 (ppm)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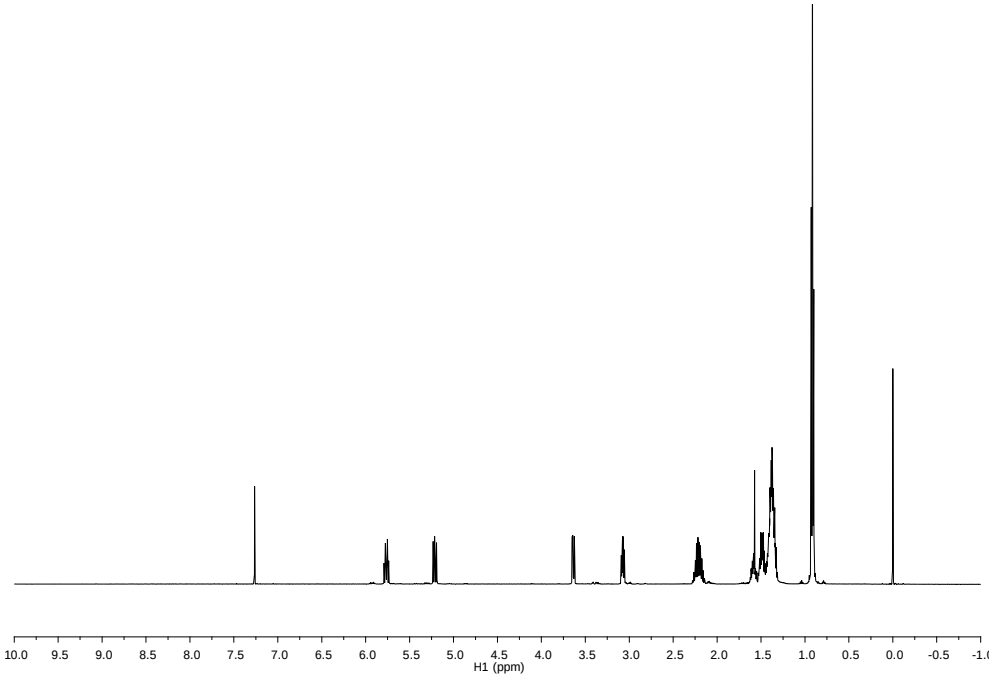
Bu

4.8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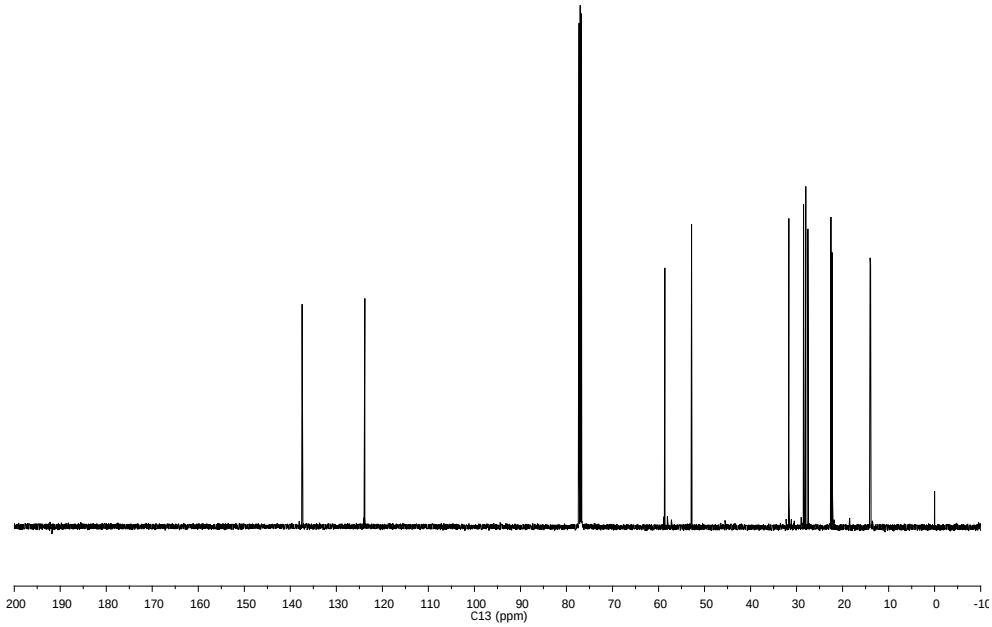
H1 (ppm)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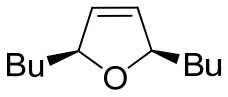
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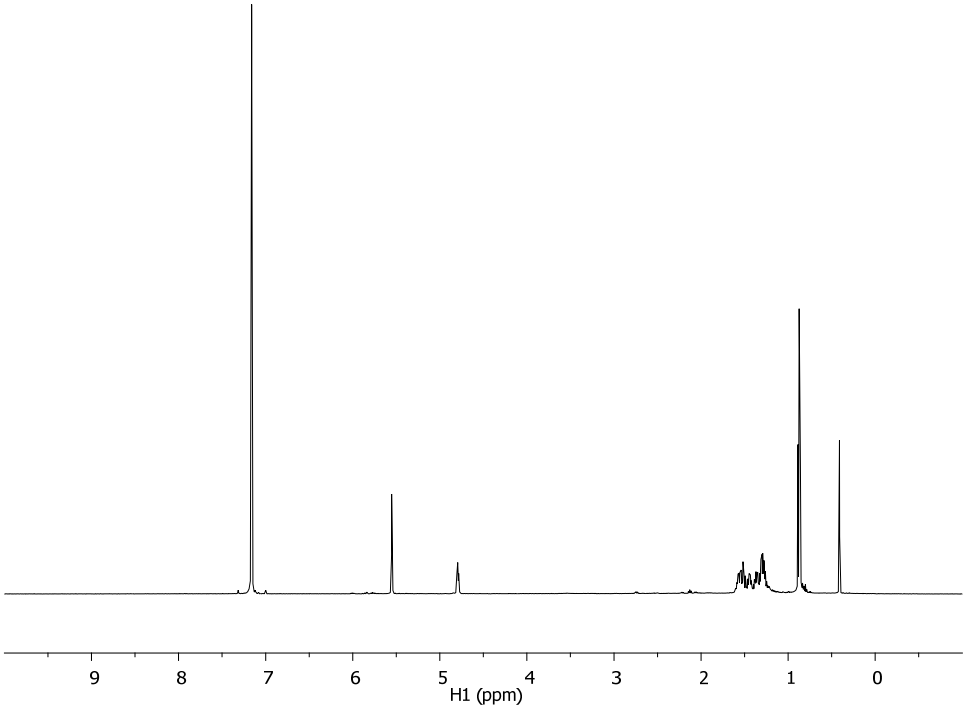
O
Bu

4.9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5
4
3
2
1
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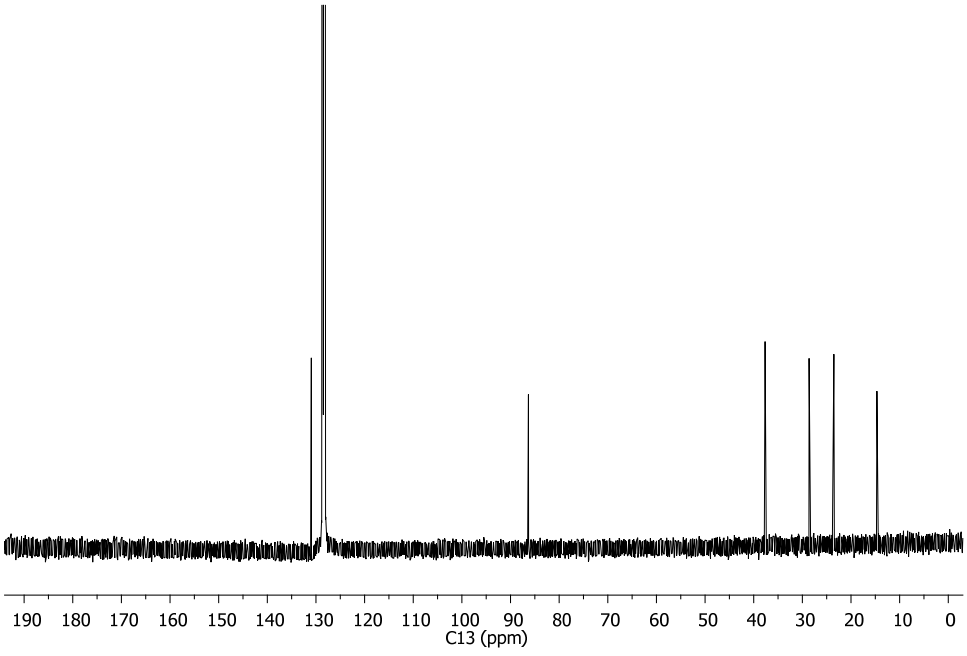
H1 (ppm)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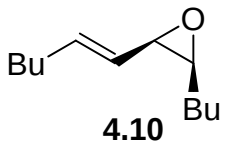
O
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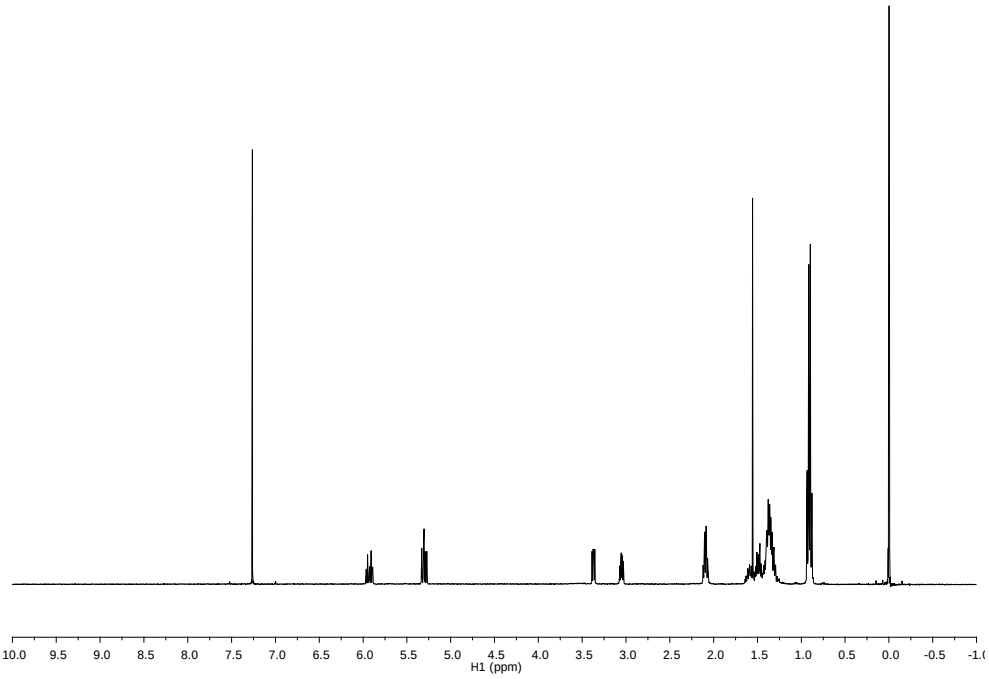
4.10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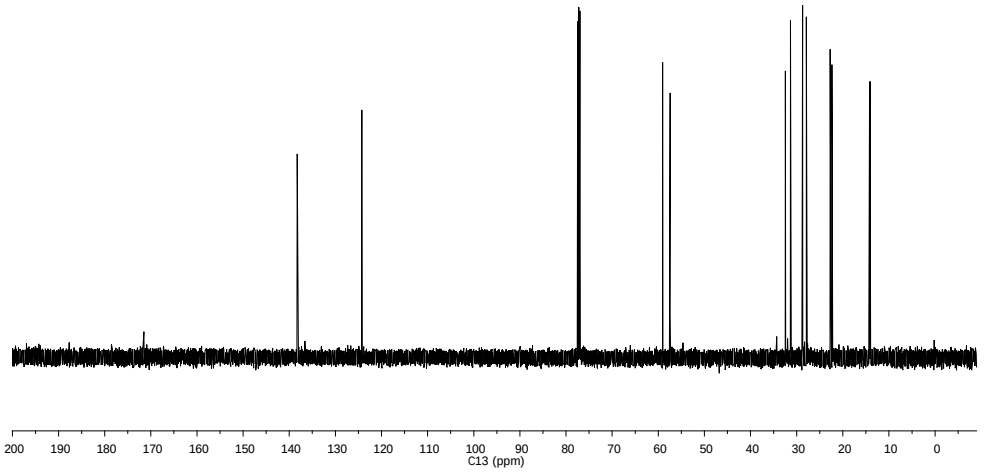
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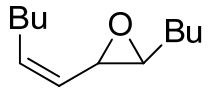
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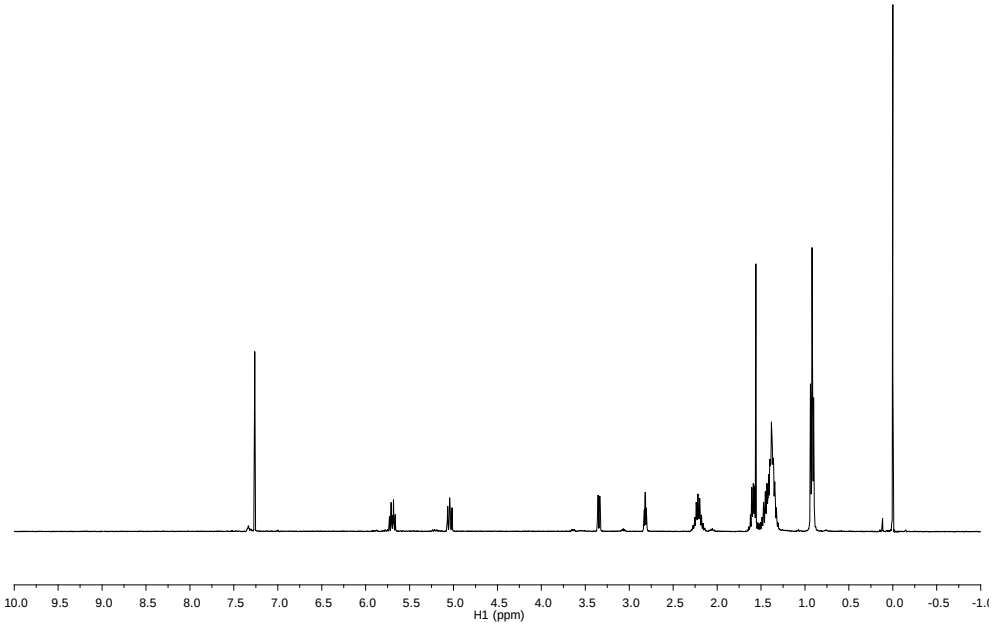
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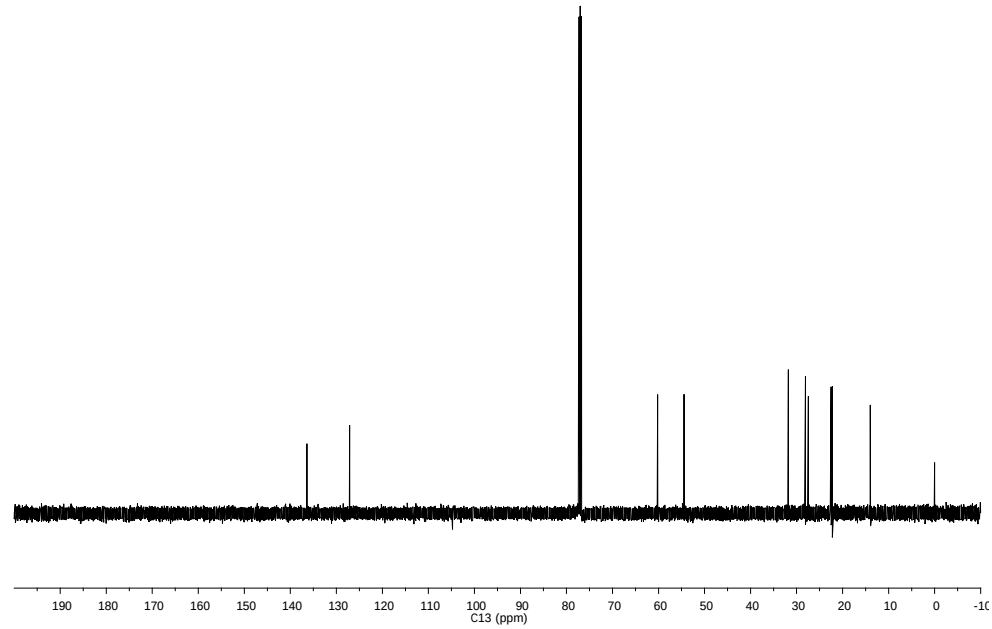
H1 (ppm)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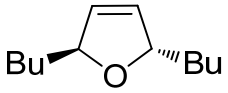
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O
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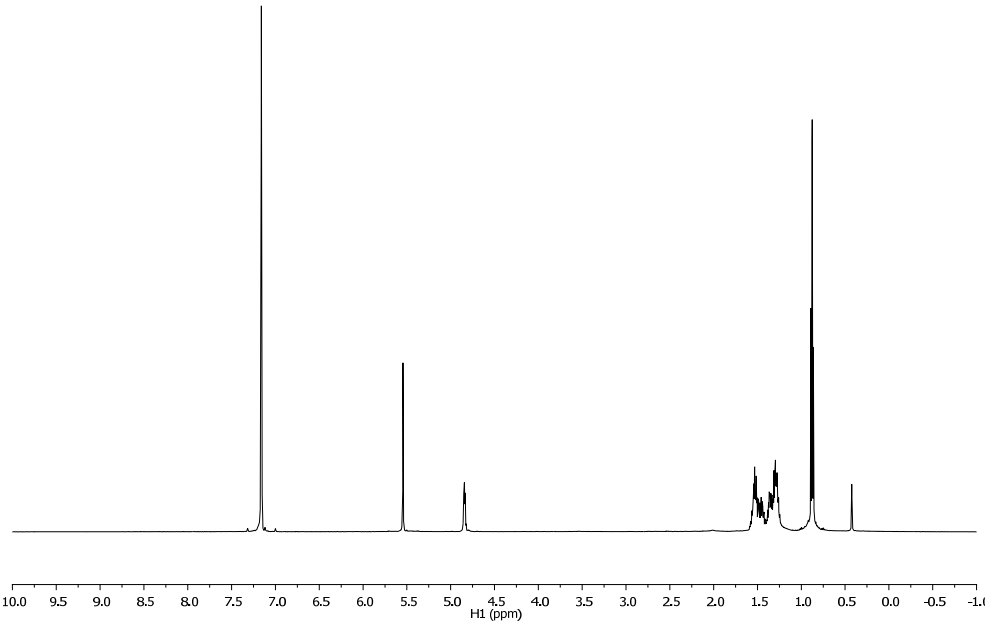
4.12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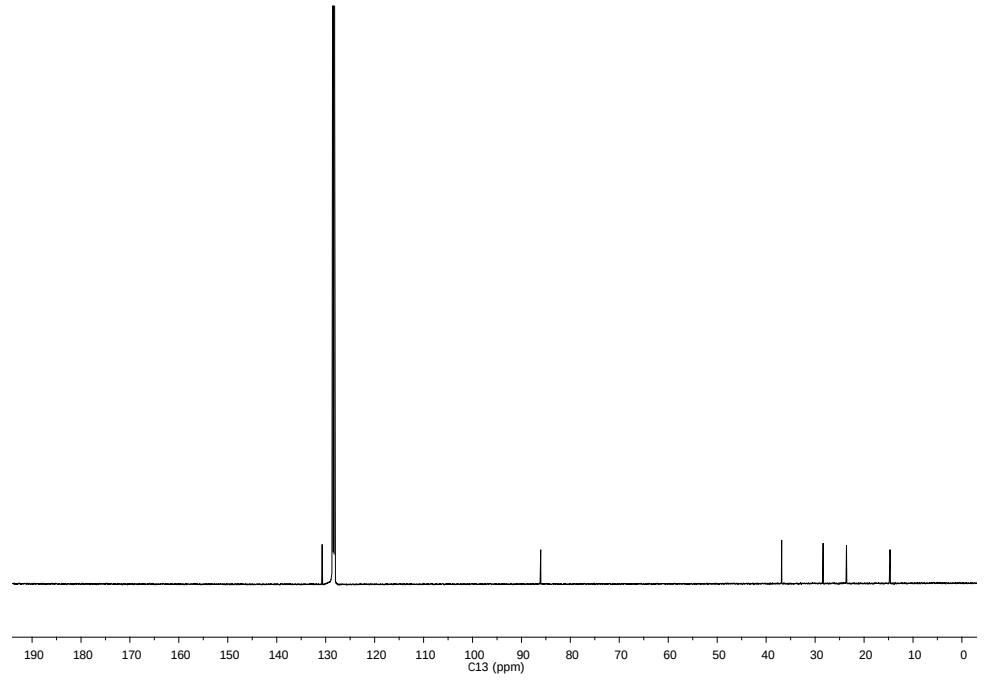
H1 (ppm)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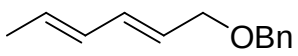
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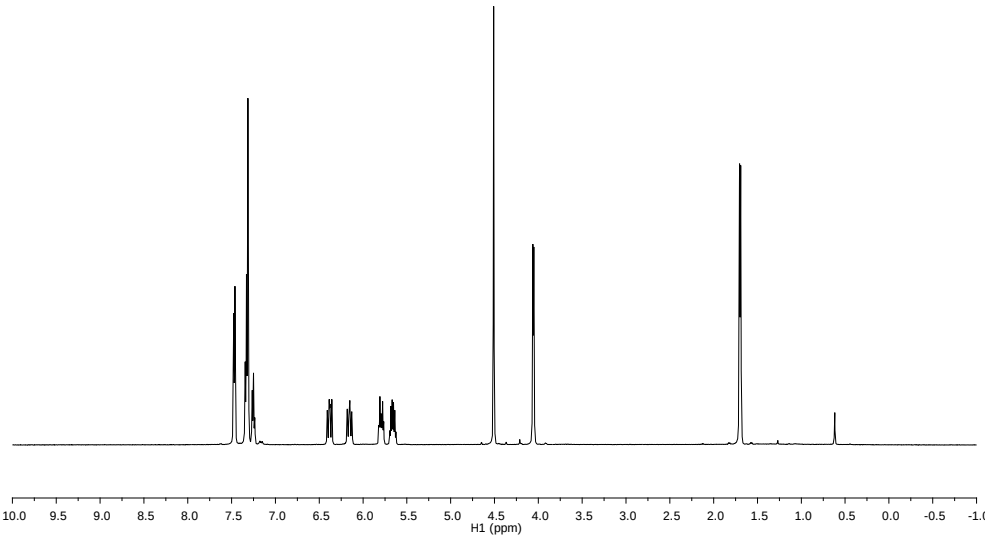
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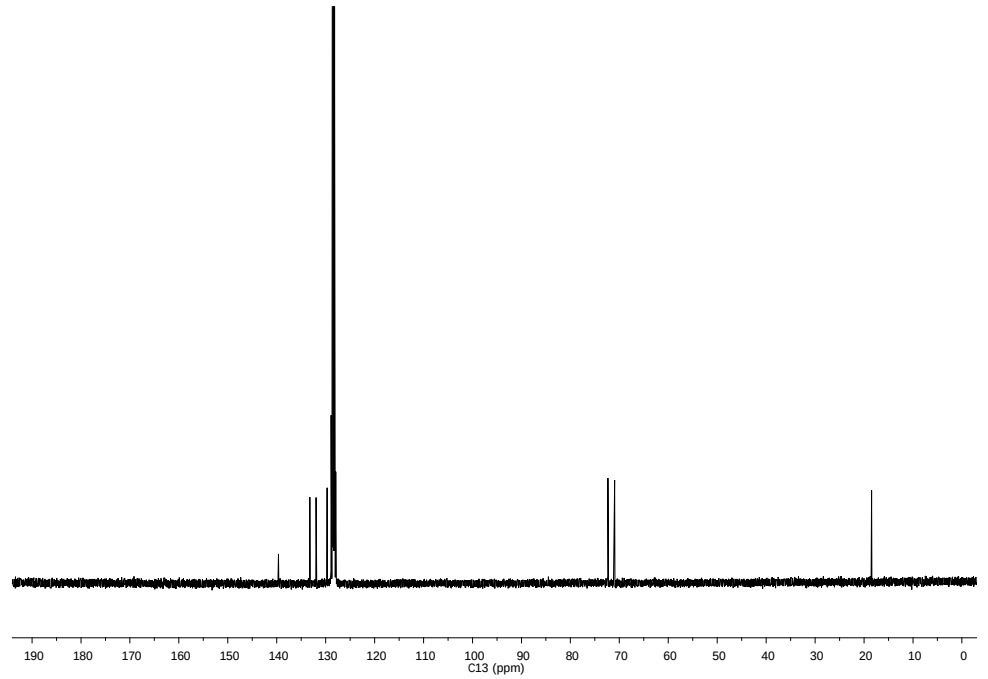
H1 (ppm)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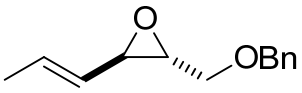
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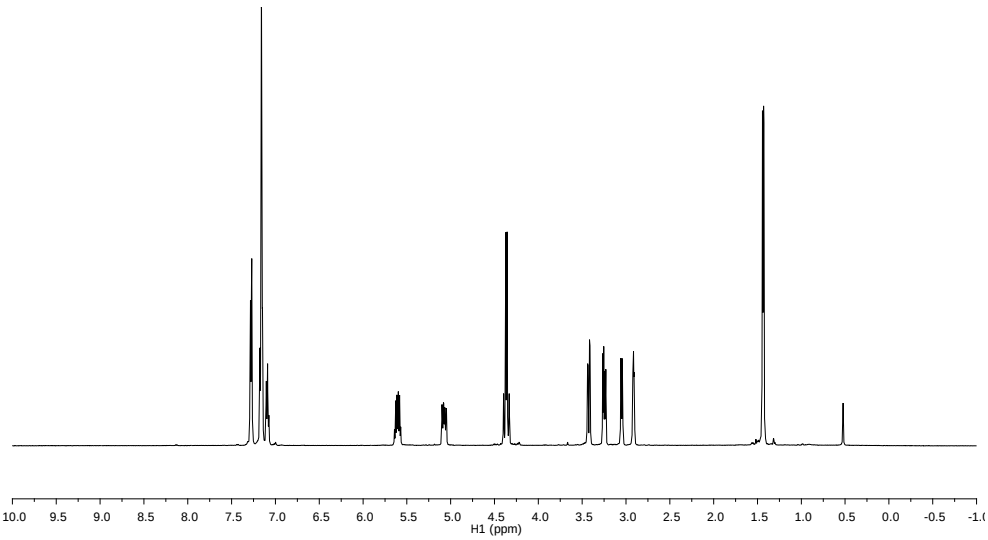
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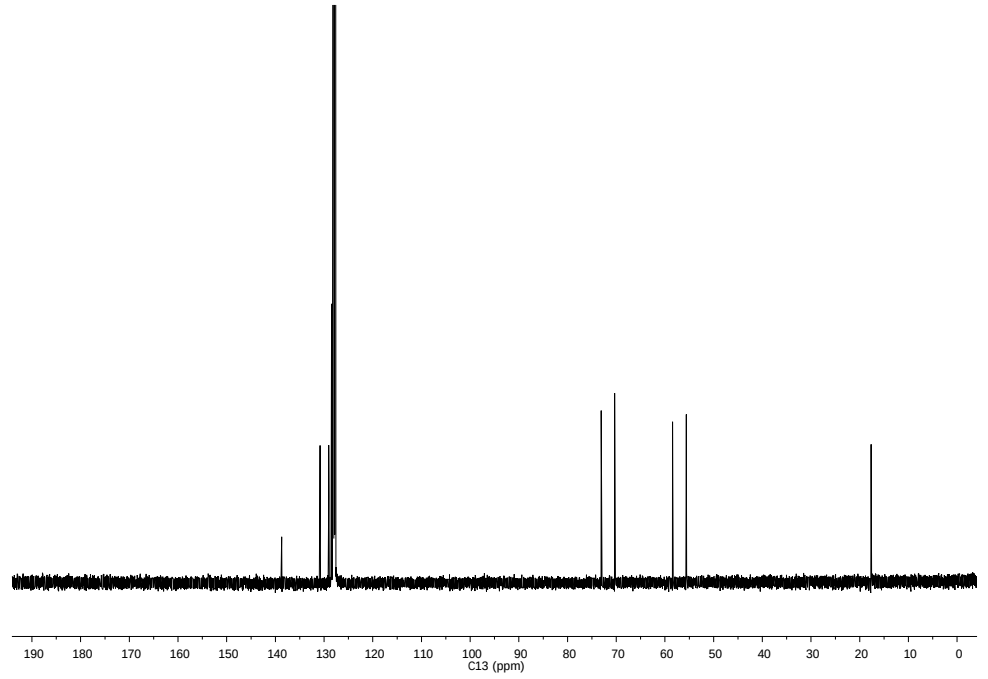
H1 (ppm)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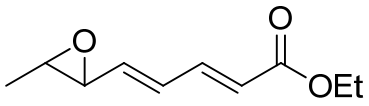
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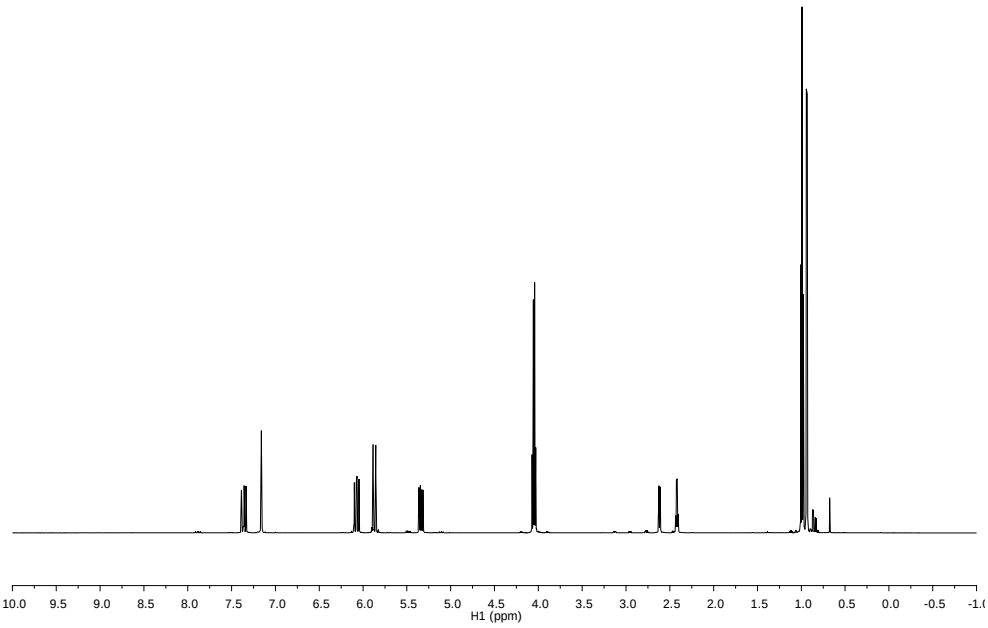
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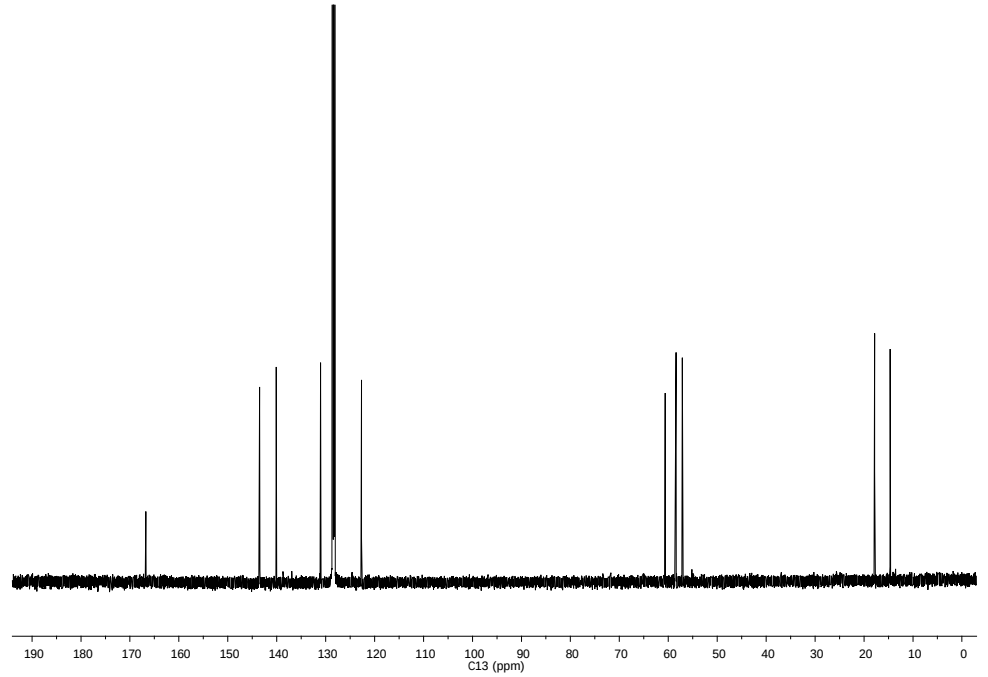
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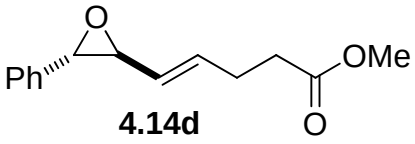
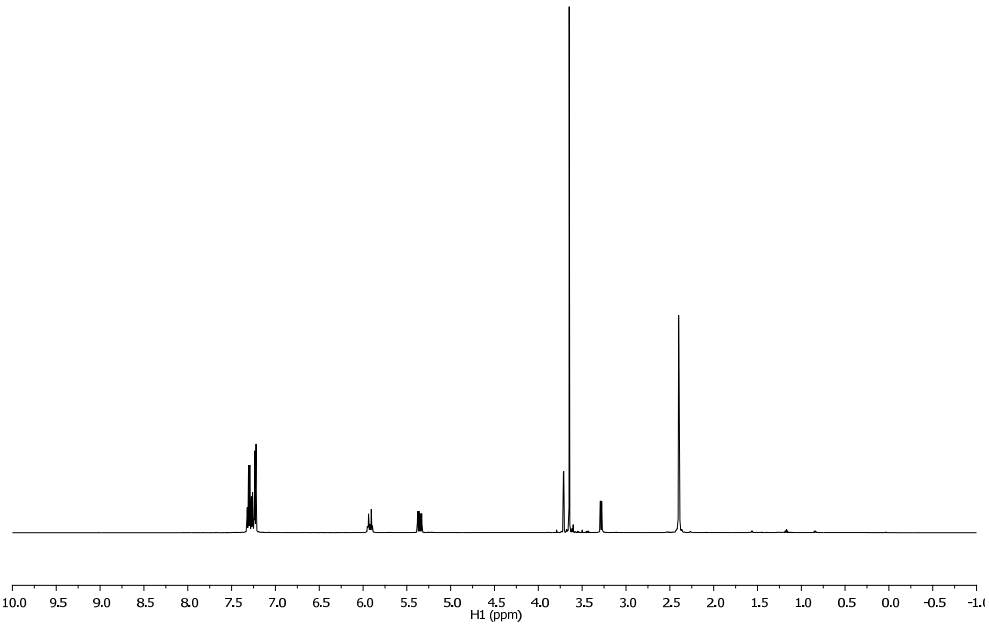
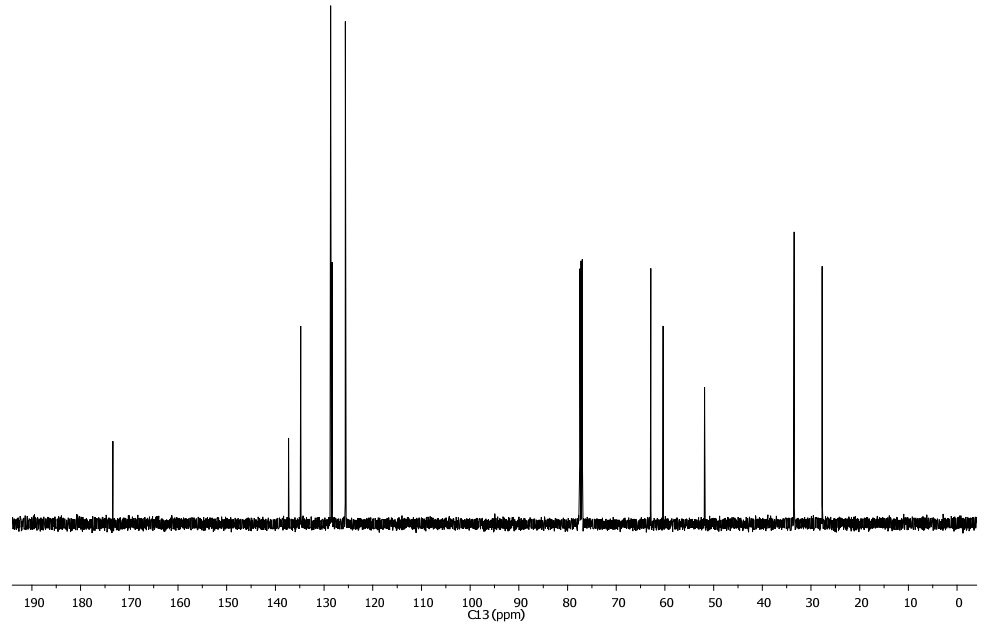
C13 (ppm)


O
Ph
OMe
O

4.14d


10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
H1 (ppm)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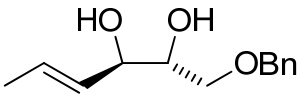
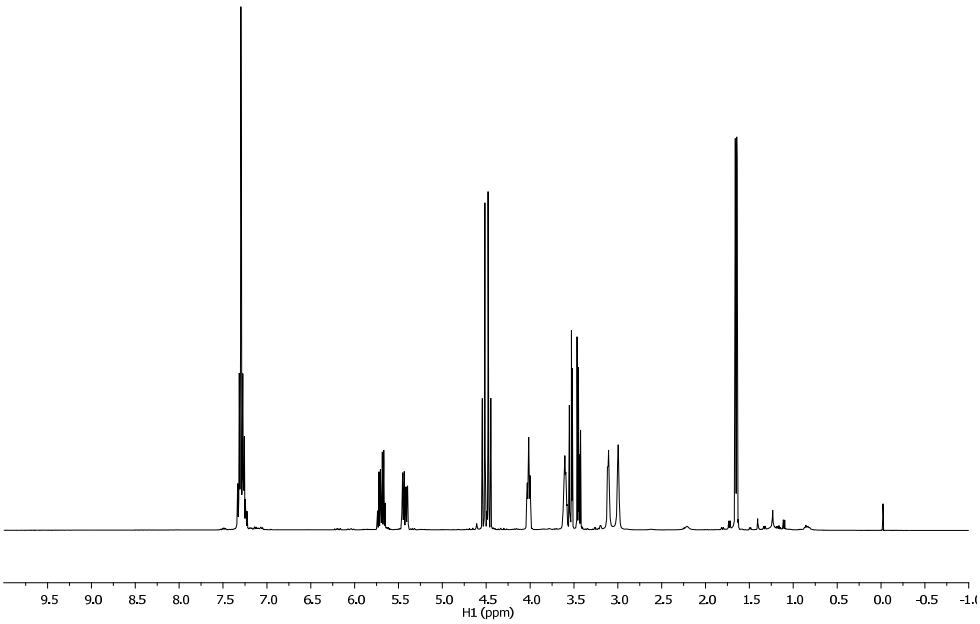
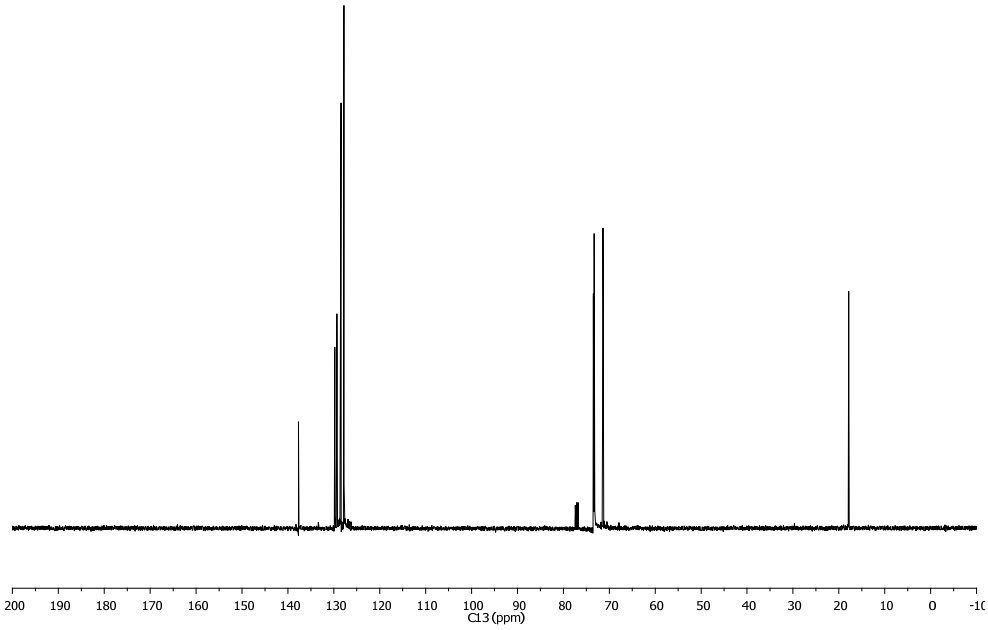
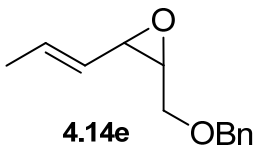
C13 (ppm)


HO
OH
OBn

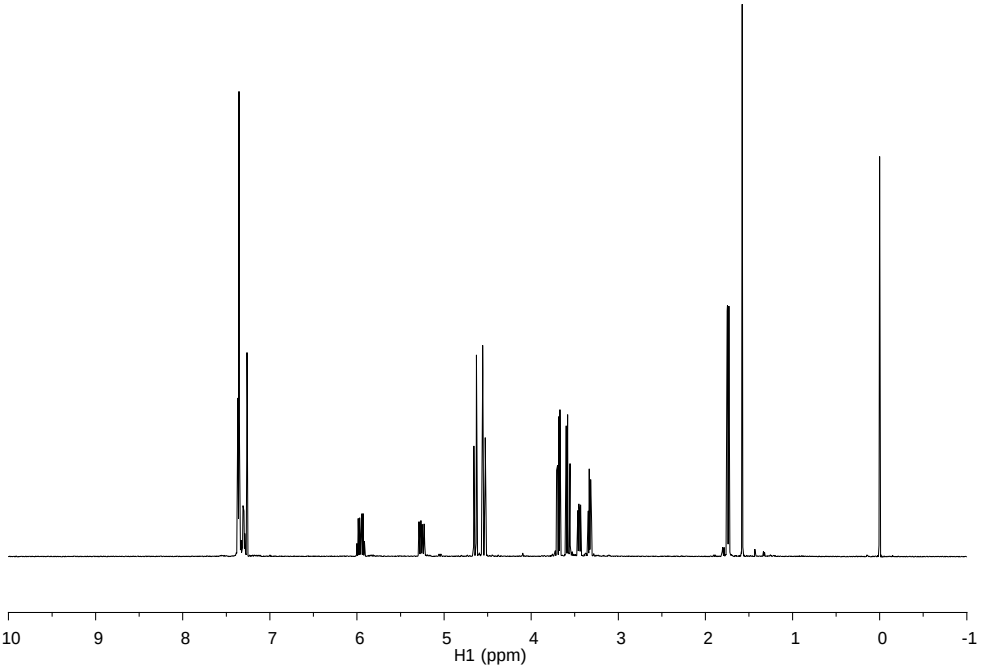
4.44

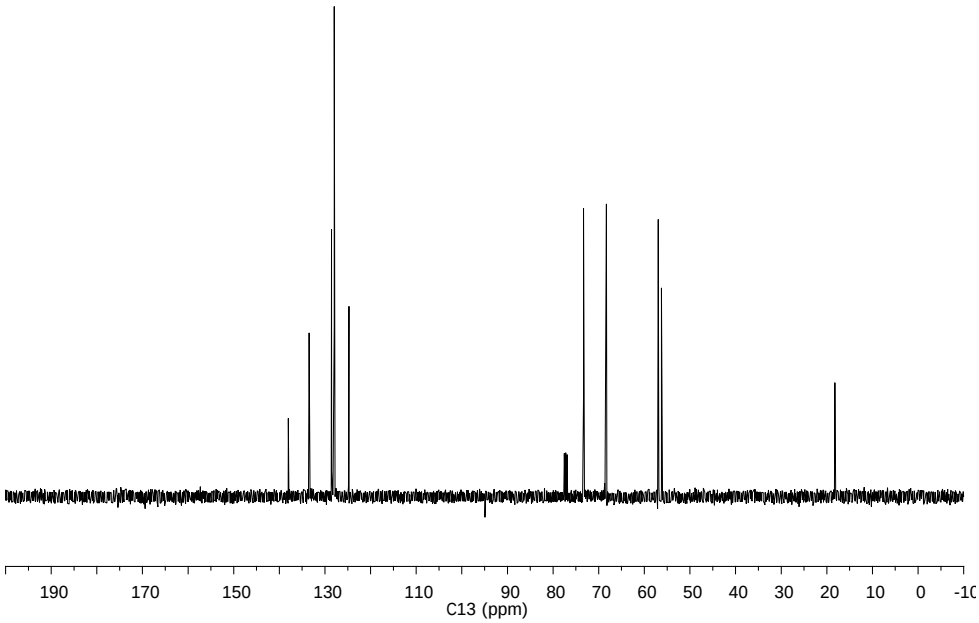

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
H1 (ppm)

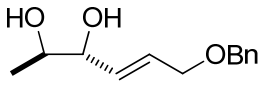

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
C13 (ppm)


O
OBn

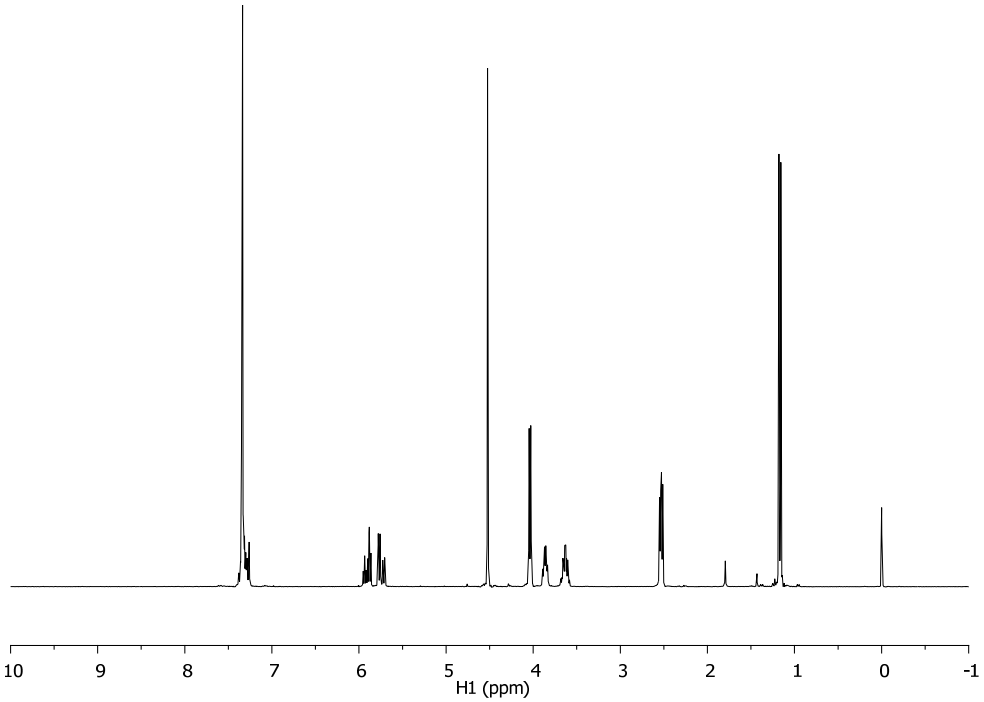
4.14e

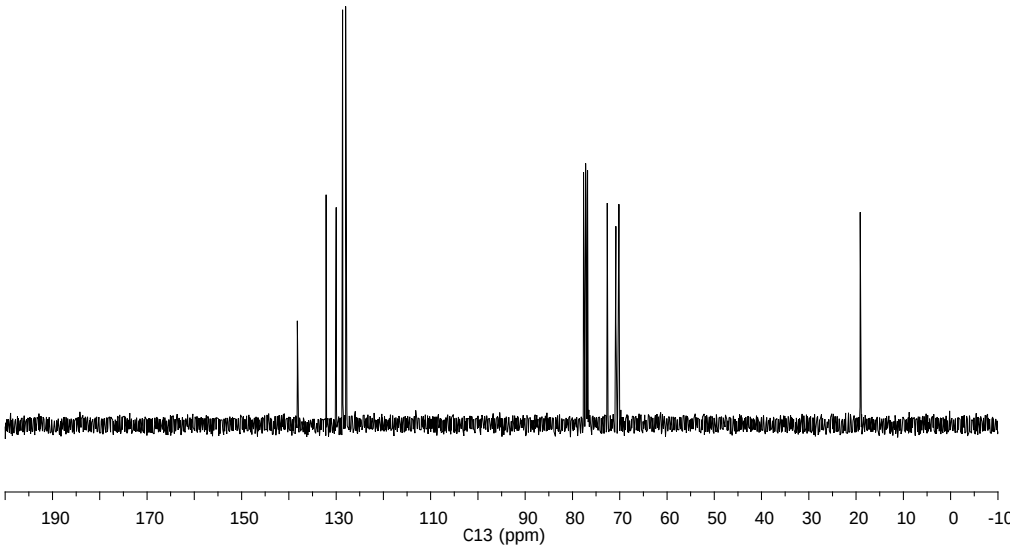

10
9
8
7
6
5
4
3
2
1
0
-1
H1 (ppm)

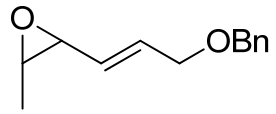

190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
C13 (ppm)


HO
OH
OBn

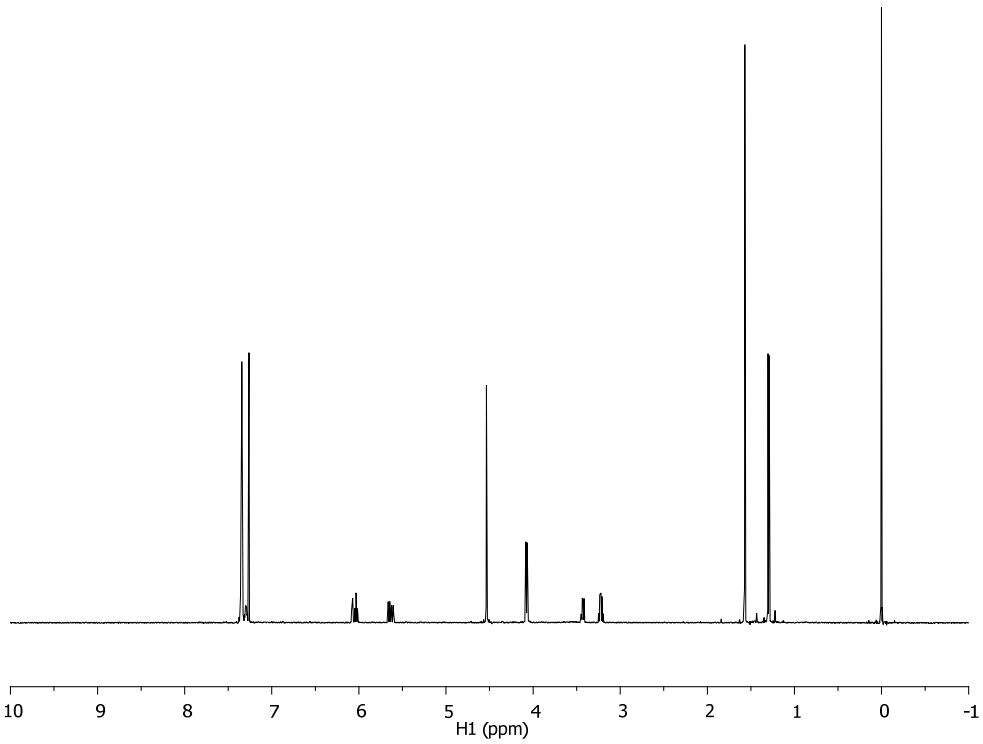
4.45

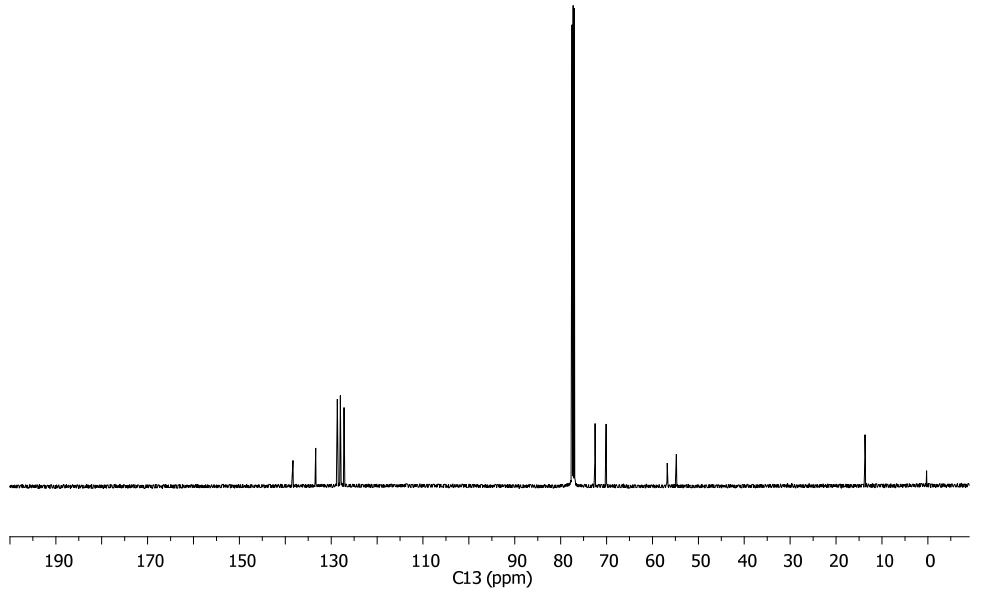

10
9
8
7
6
5
4
3
2
1
0
-1
H1 (ppm)

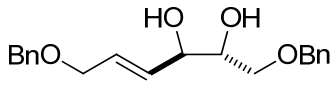

190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
C13 (ppm)


O
OBn

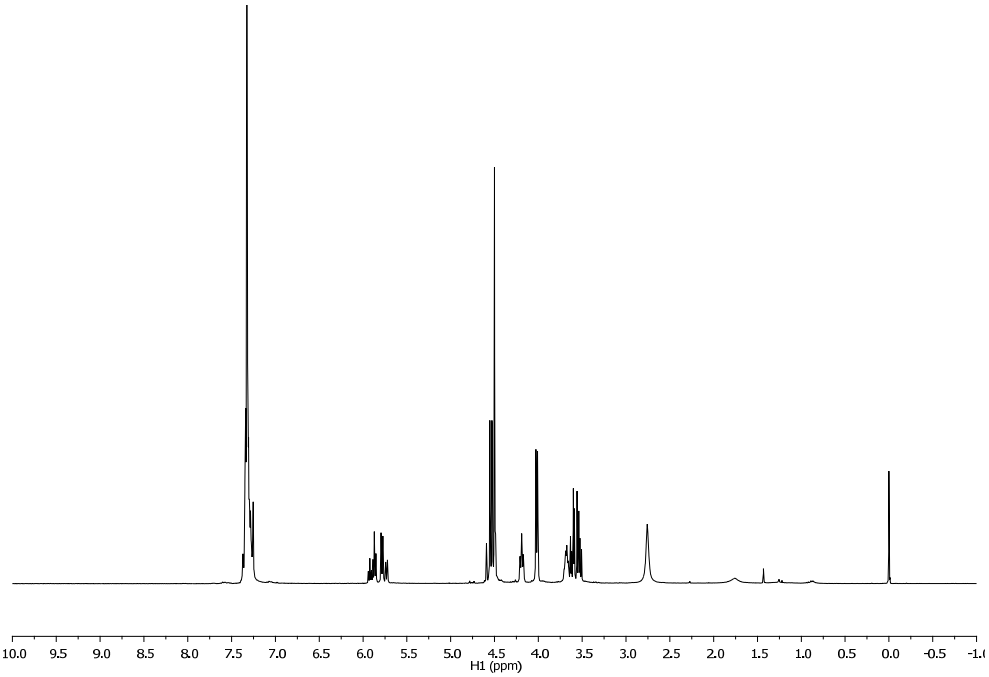
4.14f

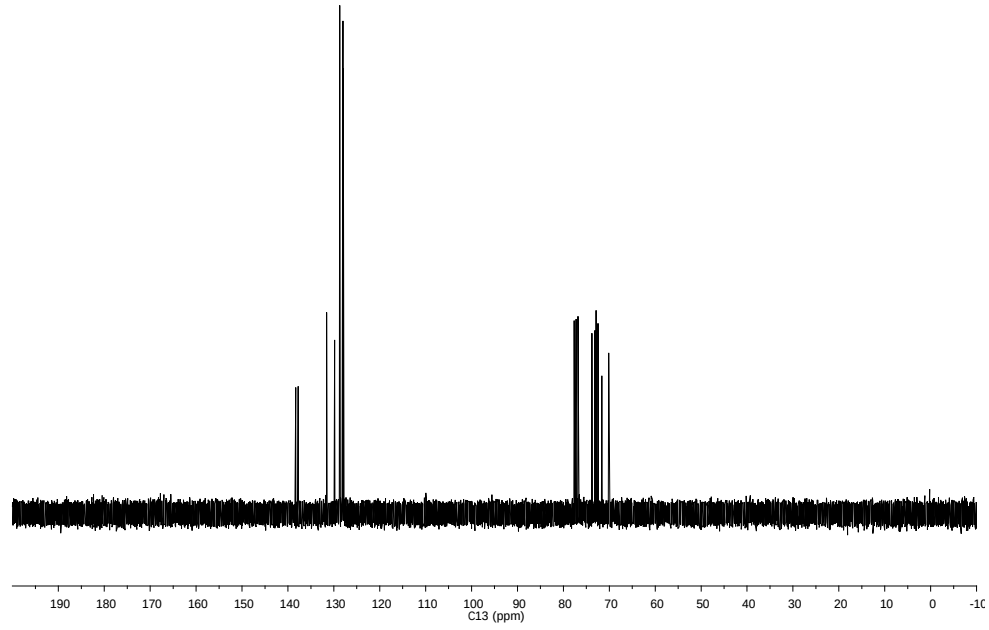

10
9
8
7
6
5
4
3
2
1
0
-1
H1 (ppm)


190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
C13 (ppm)


HO
OH
BnO
OBn

4.47


10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
H1 (ppm)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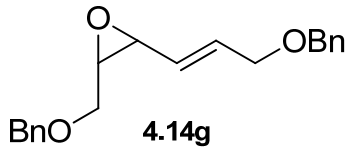
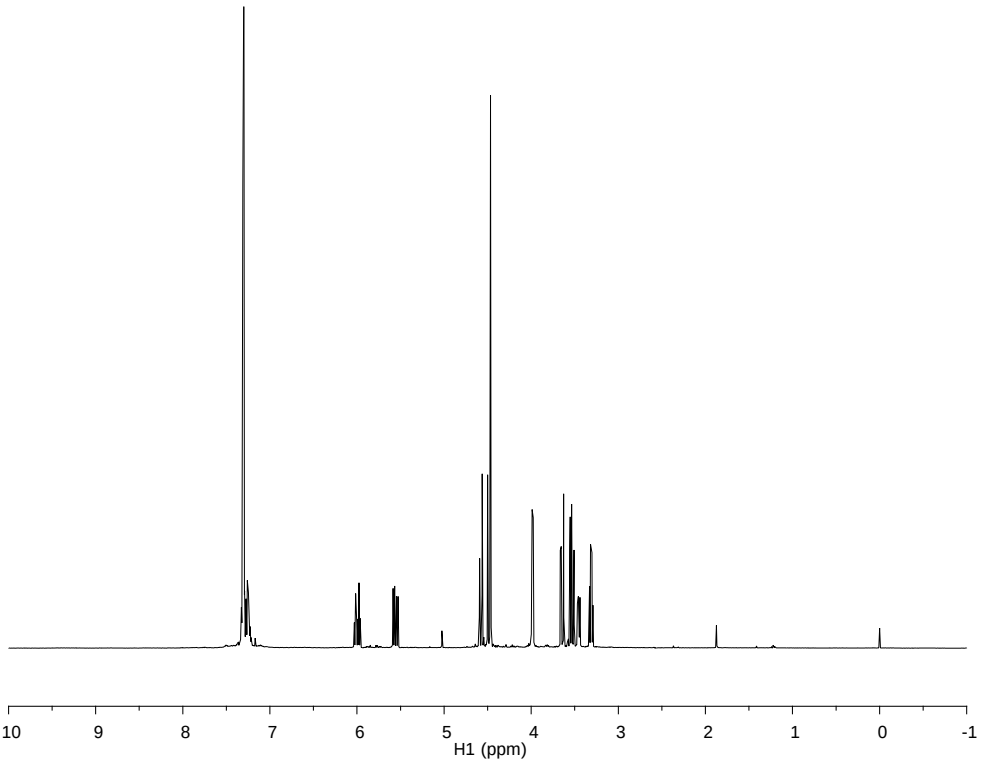
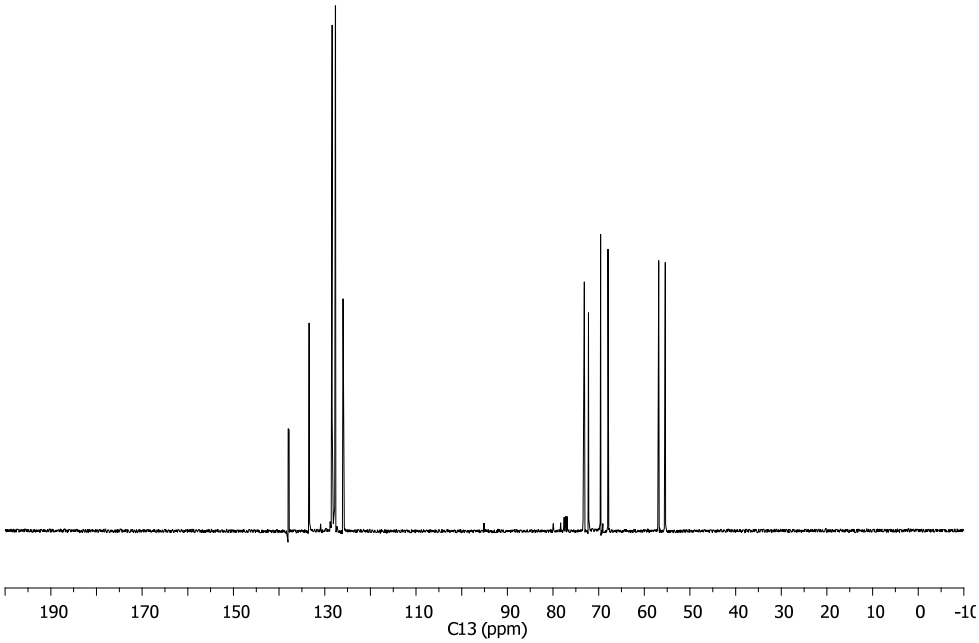
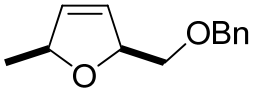
C13 (ppm)


O
OBn
BnO

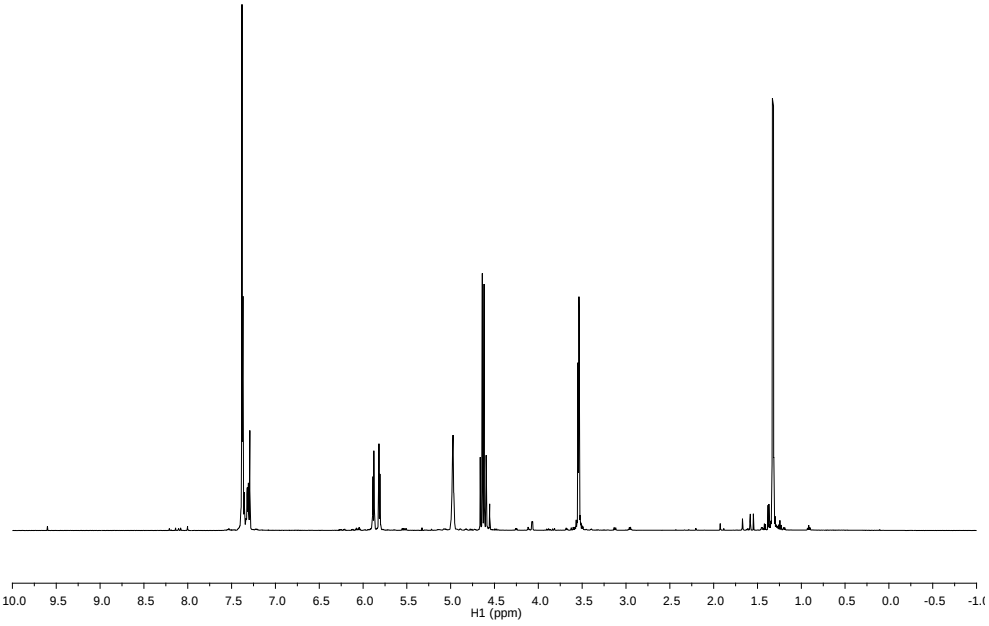
4.14g


10
9
8
7
6
5
4
3
2
1
0
-1
H1 (ppm)


190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
C13 (ppm)


OBn
O

4.15a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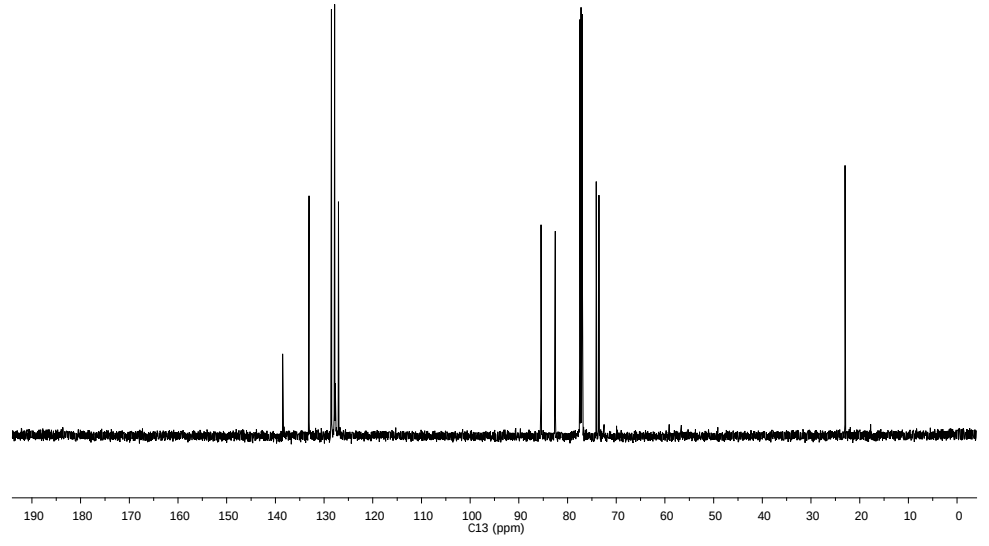
H1 (ppm)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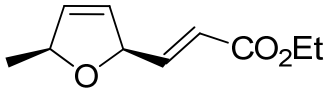
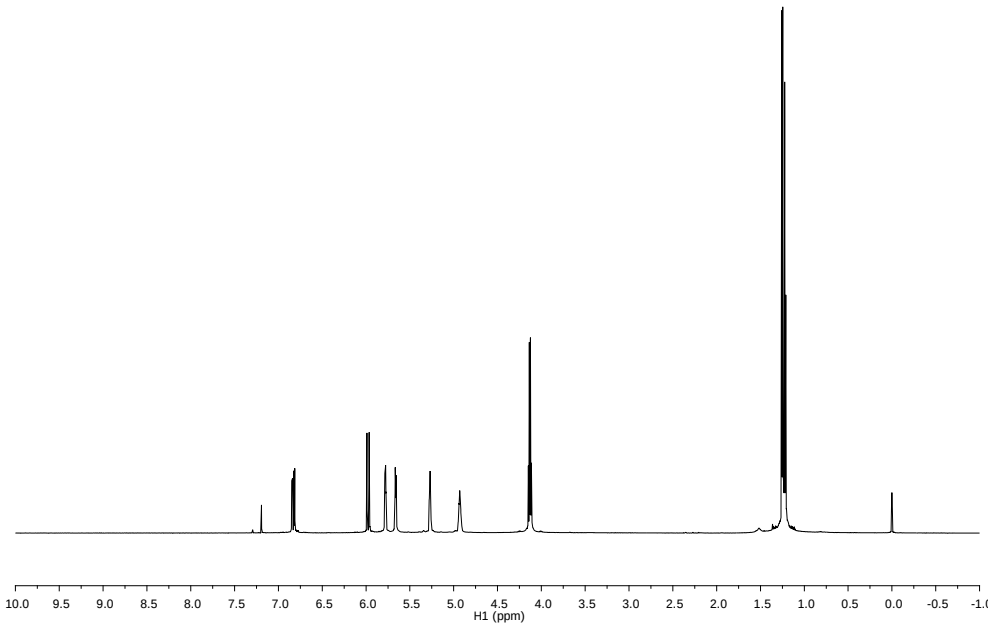
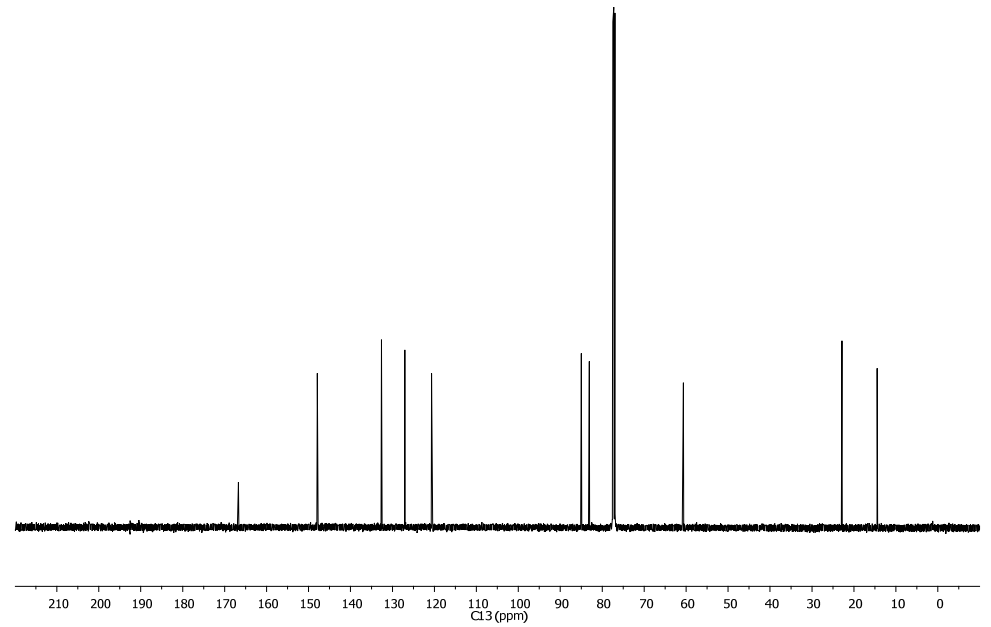
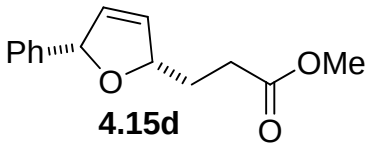
C13 (ppm)


CO2Et
O

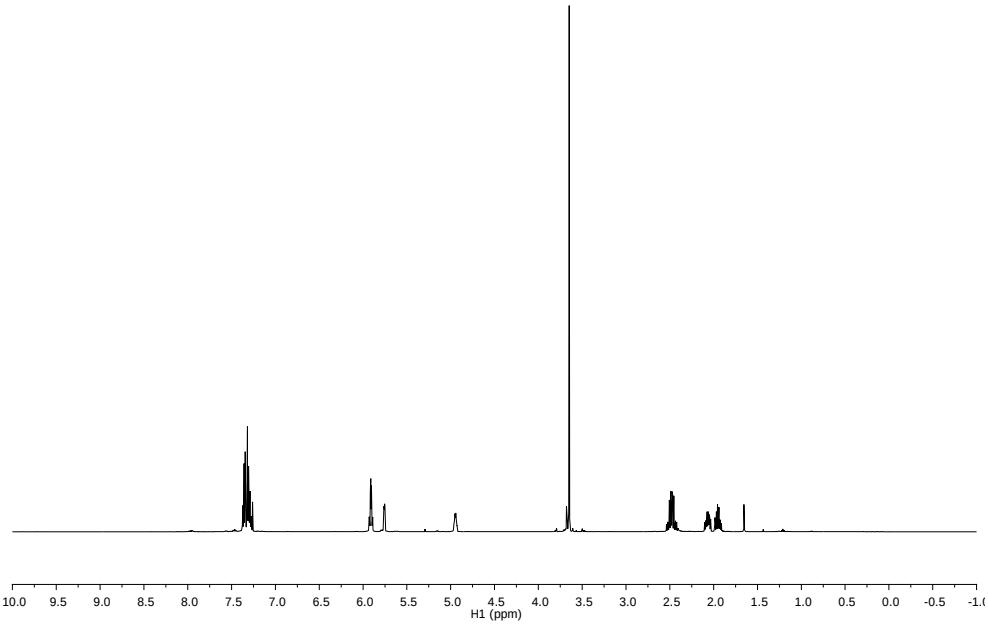
4.15c


10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
H1 (ppm)


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
C13 (ppm)


Ph
O
OMe
O

4.15d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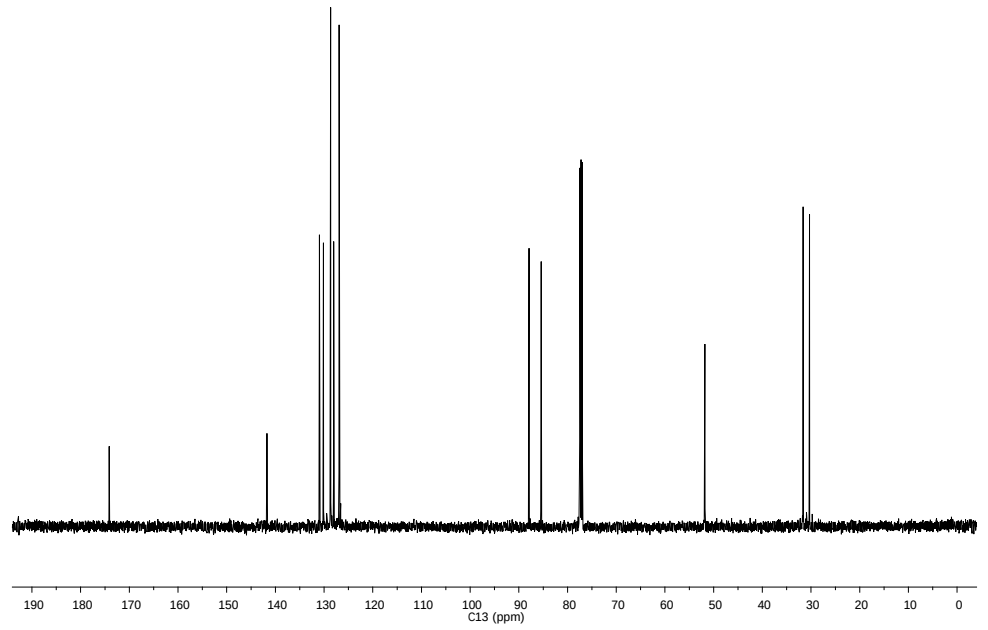
H1 (ppm)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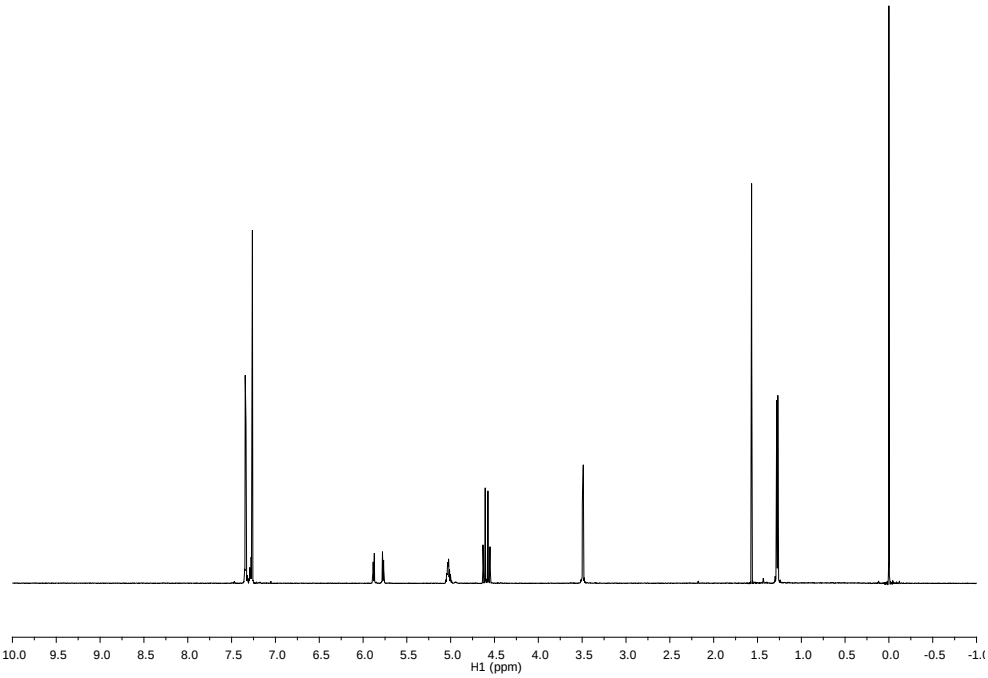
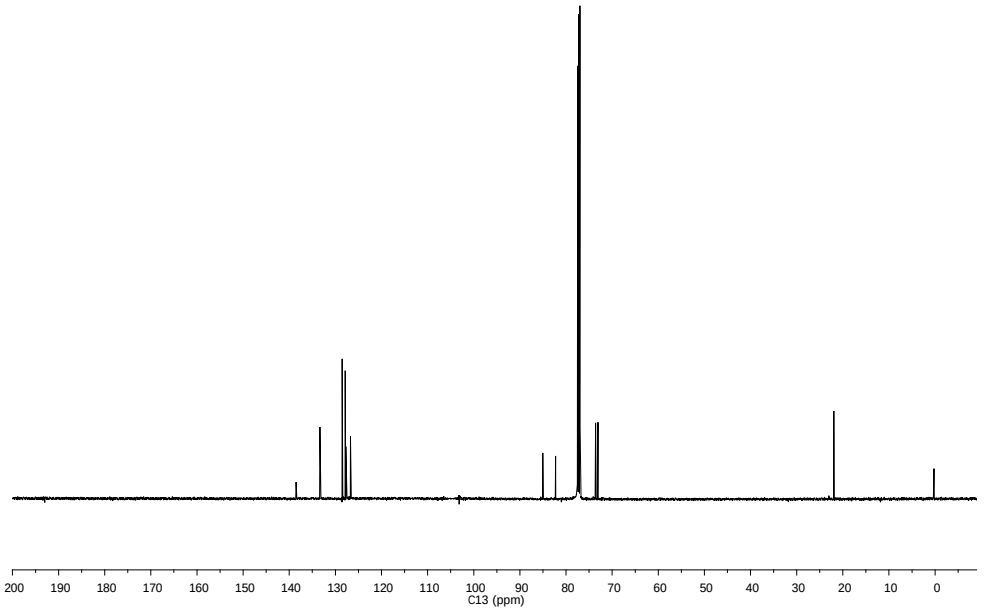
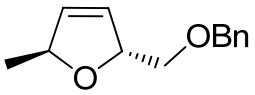
C13 (ppm)


OBn
O

4.15e

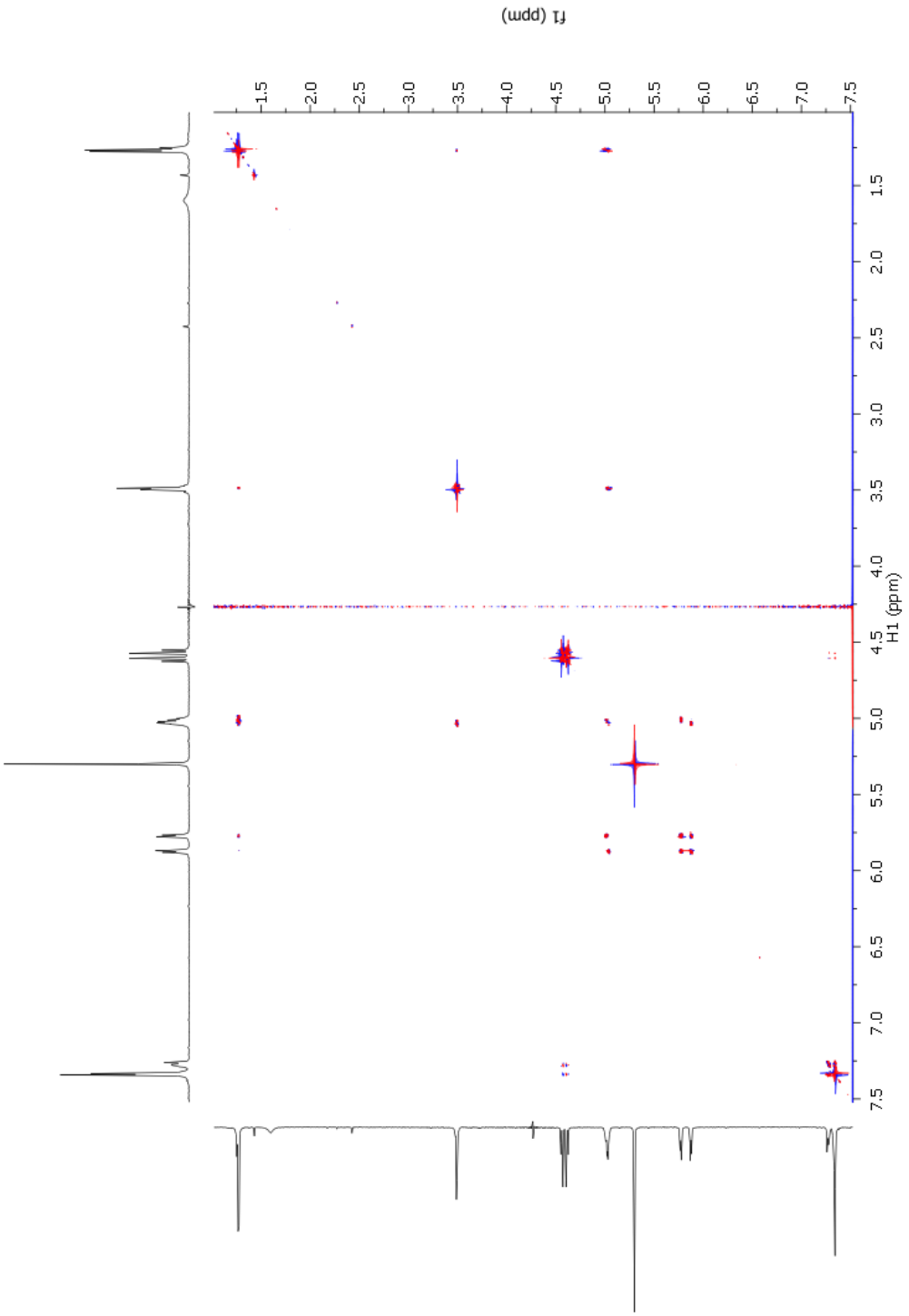

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
H1 (ppm)

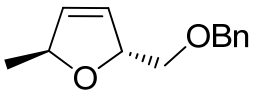

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
C13 (ppm)



4.15e

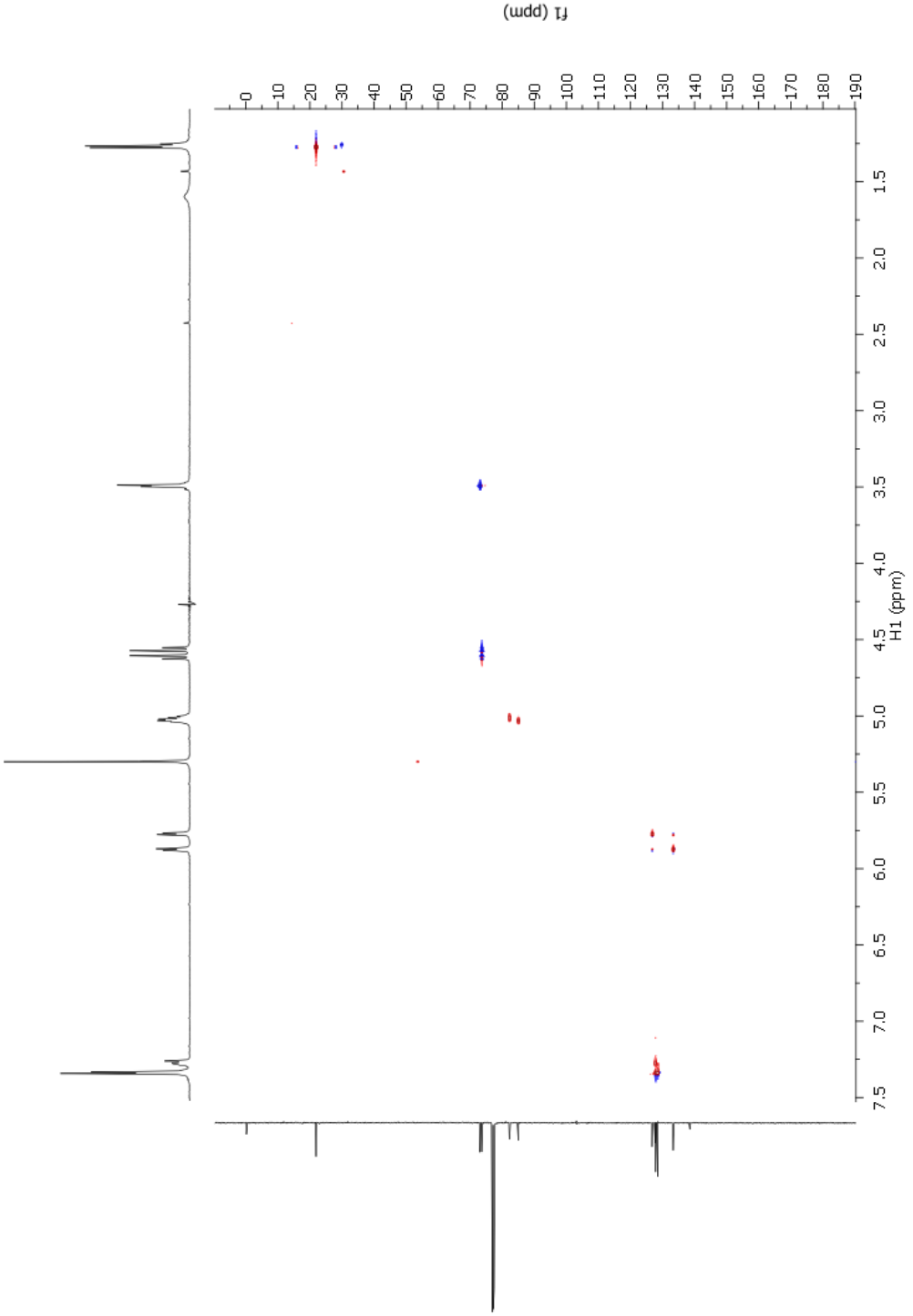
COSY

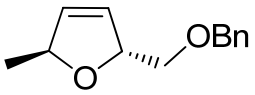




4.15e

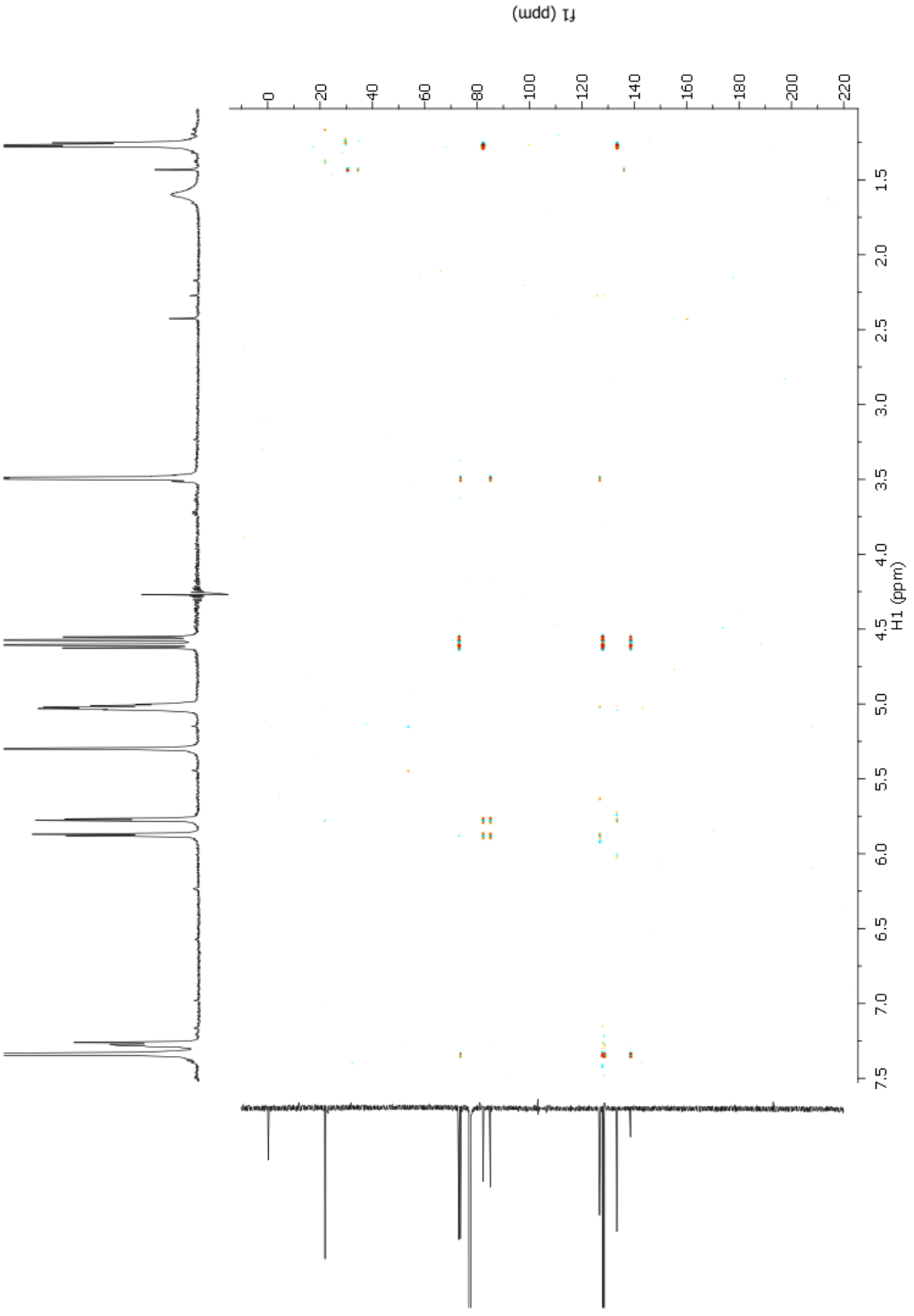
HSQC




OBn
O

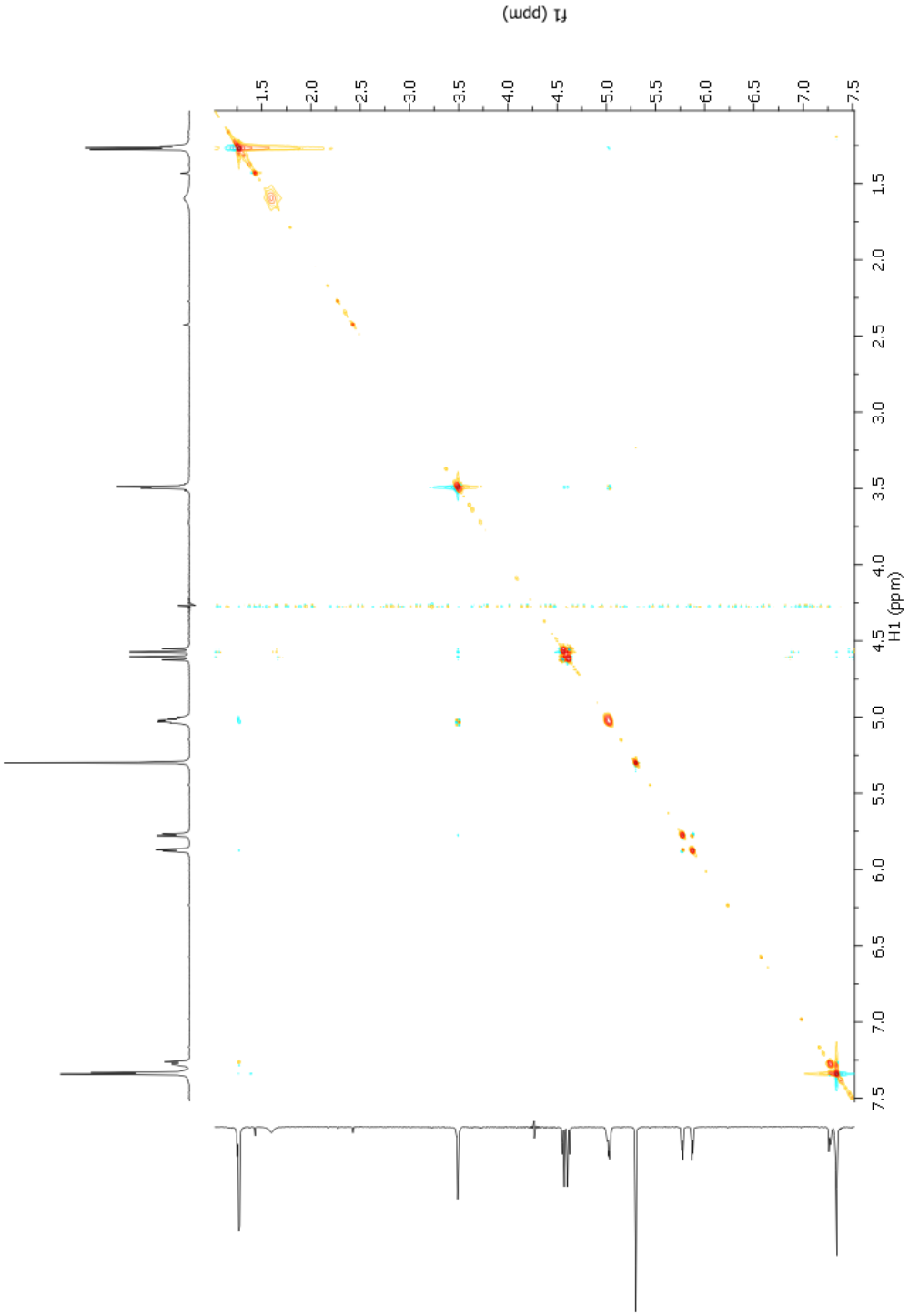
4.15e

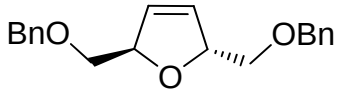
HMBC


f1 (ppm)
0
20
40
60
80
100
120
140
160
180
200
220
H1 (ppm)
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5

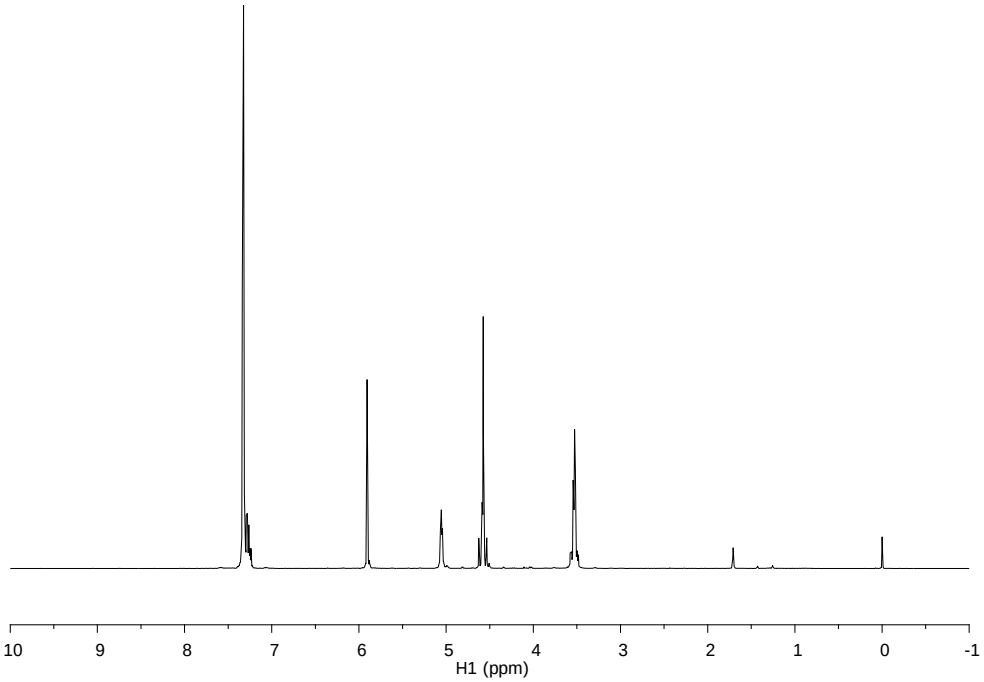
4.15e

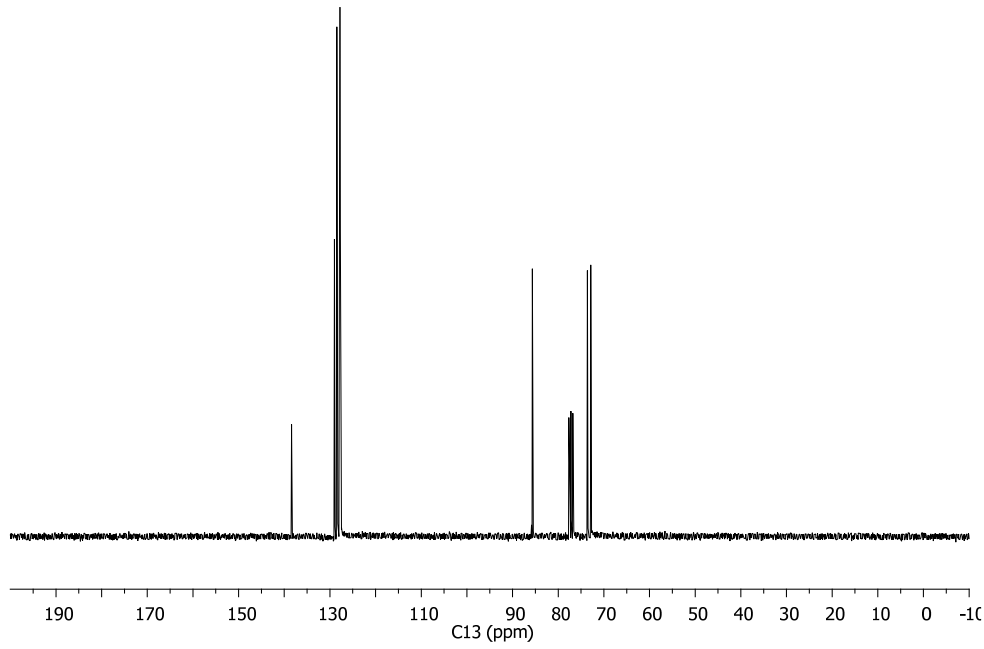
NOESY

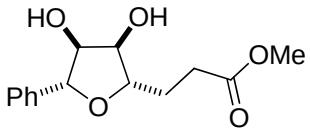



BnO
OBn
O

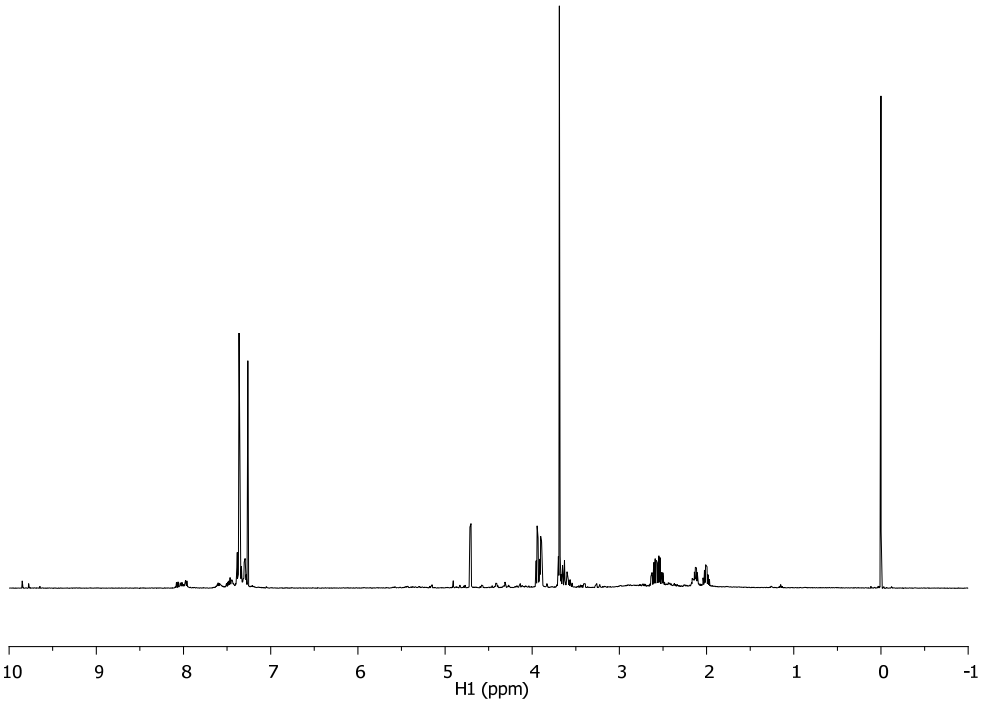
4.15g

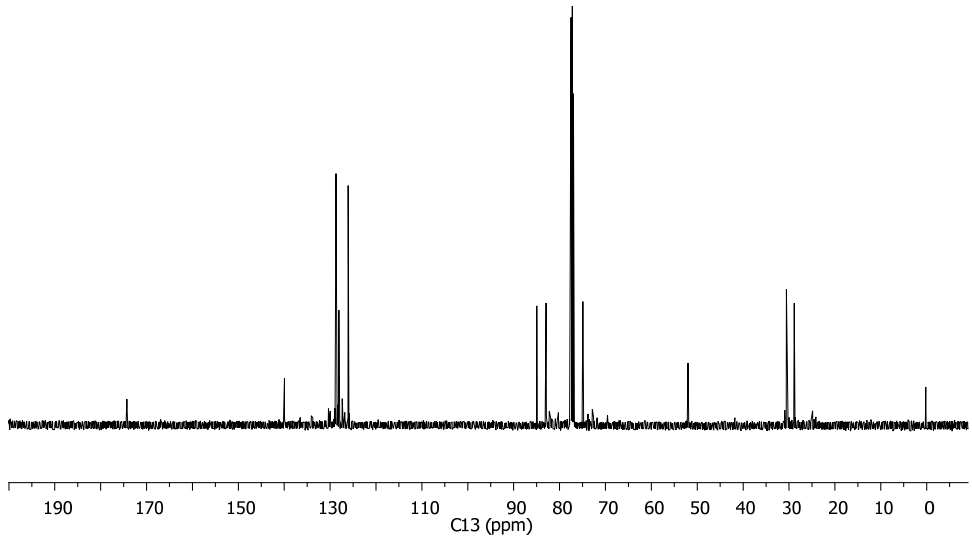

10
9
8
7
6
5
4
3
2
1
0
-1
H1 (ppm)

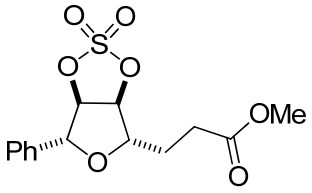

190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
C13 (ppm)


HO
OH
OMe
Ph
O
O

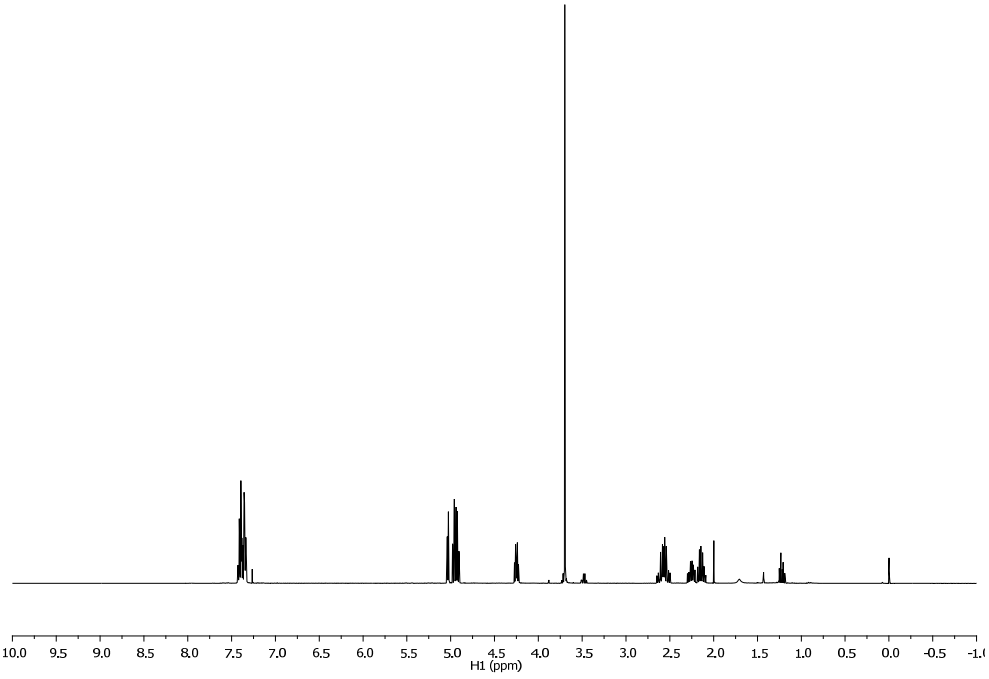
4.48

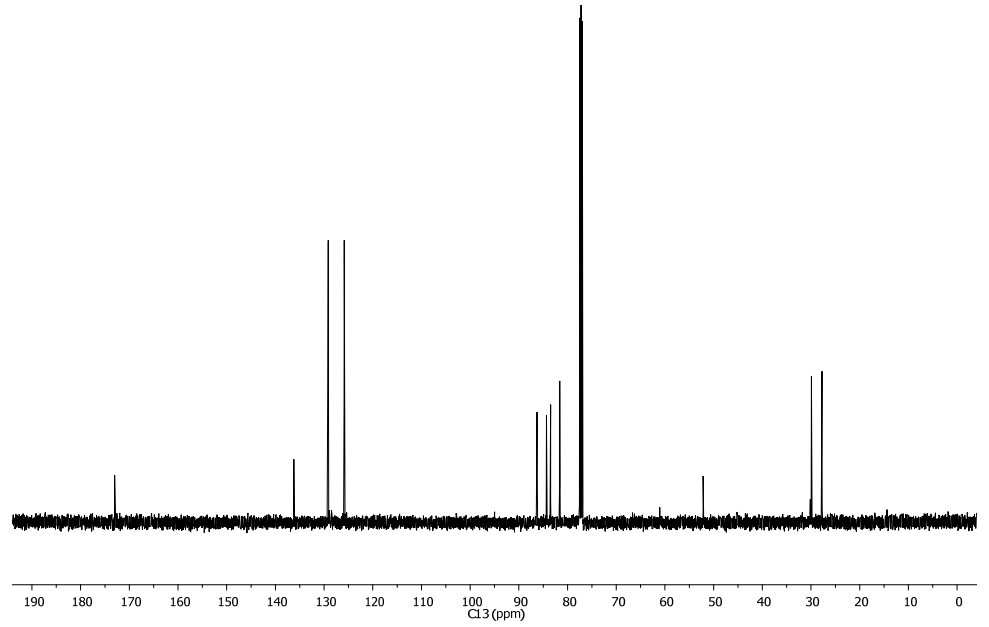

10
9
8
7
6
5
4
3
2
1
0
-1
H1 (ppm)

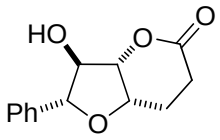

190
170
150
130
110
90
80
70
60
50
40
30
20
10
0
C13 (ppm)


O
O
S
O
O
OMe
Ph
O
O

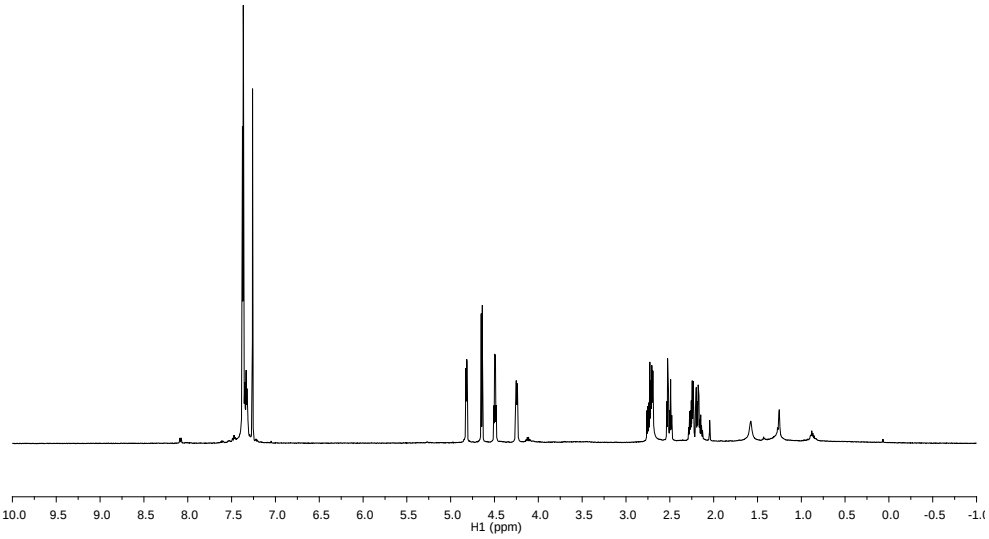
4.20

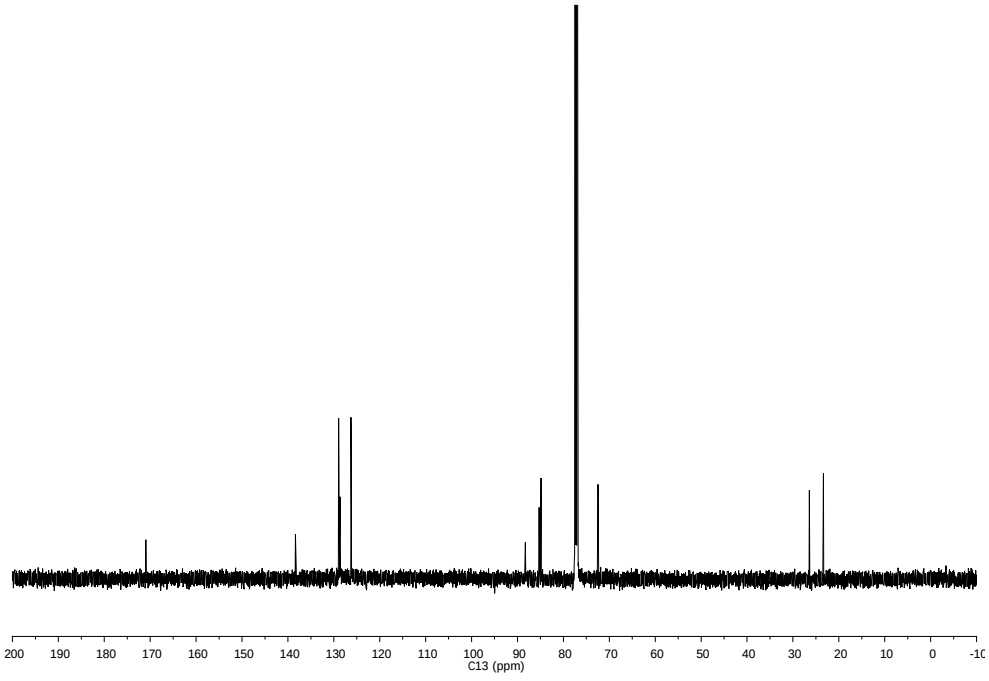

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
H1 (ppm)

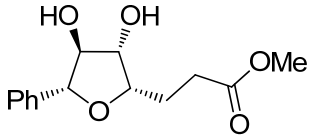

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
C13 (ppm)


HO
O
O
Ph
O

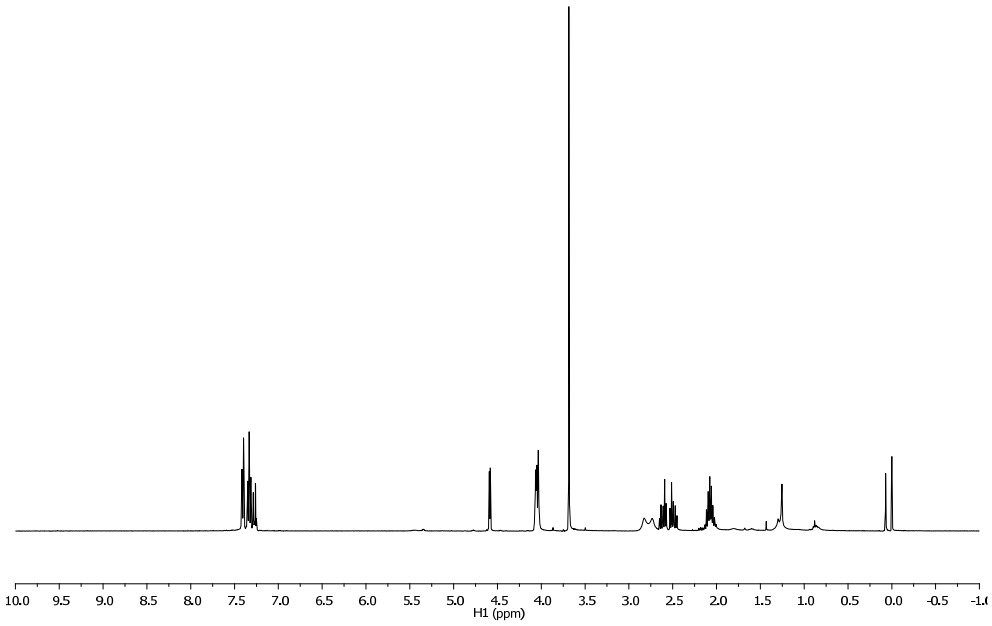
(+) 4.21

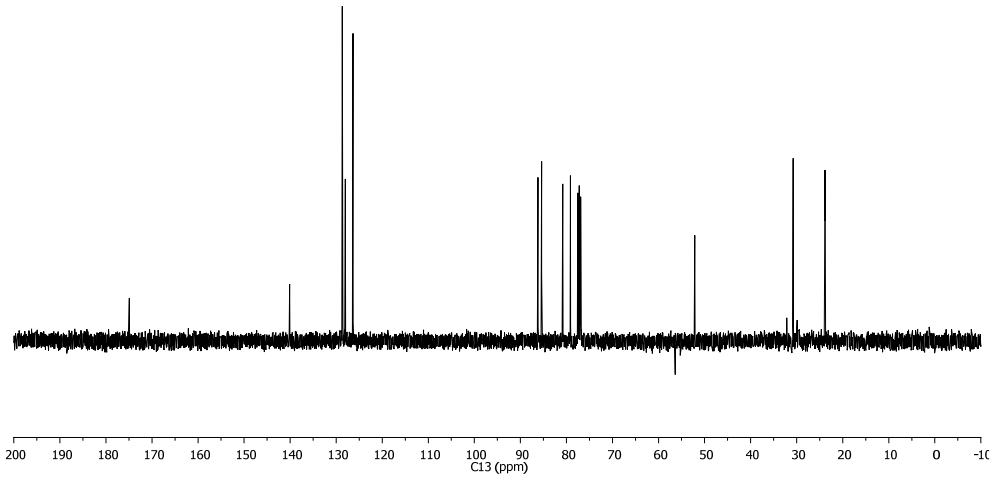

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
H1 (ppm)

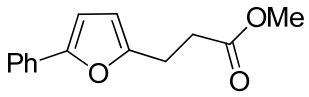

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
C13 (ppm)



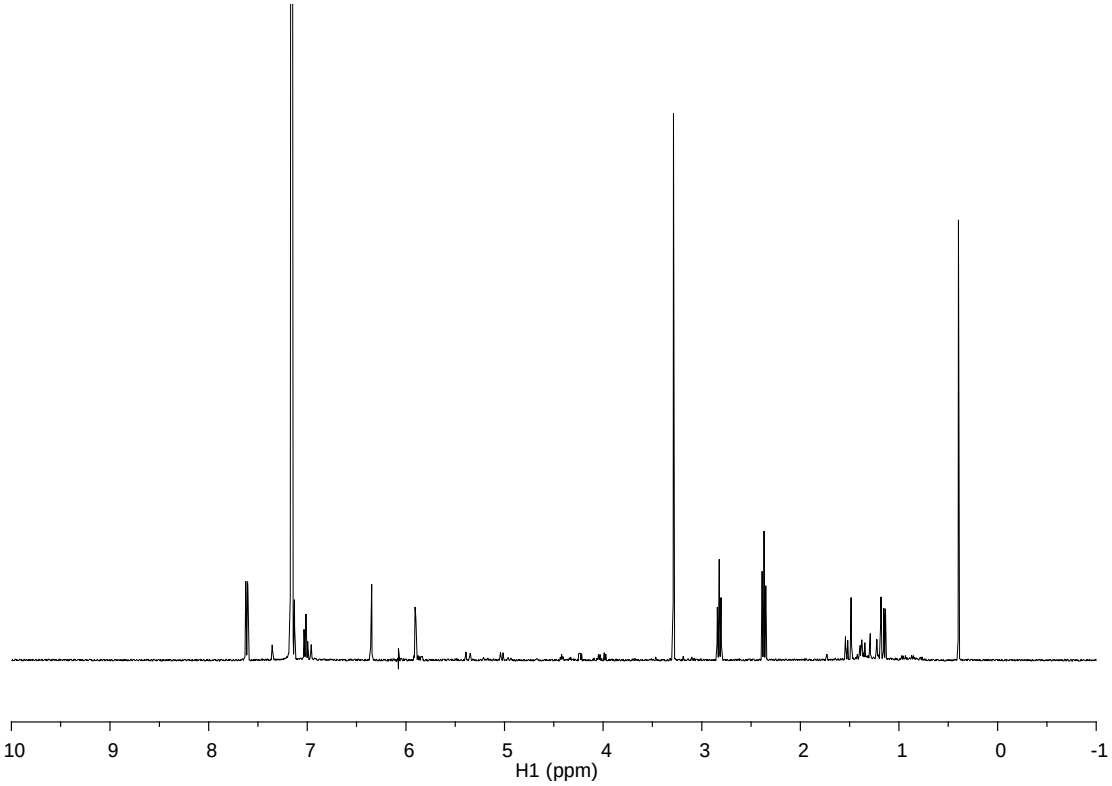
(+)-goniothalesdiol **4.22**







4.49

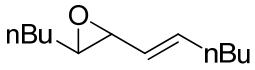


A4.3 Coordinates and Calculated Energies for Chapter 4

DFT calculations were performed with the program Gaussian03[1] by using the WebMO interface (WebMO, version 9.1.002p; www.webmo.net) for importing and constructing models.

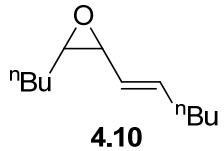
[1] Gaussian 03, Revision C.02, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, and J. A. Pople, Gaussian, Inc., Wallingford CT, 2004.

Structure	Method Basis Set	Corrected Energy (hartree)	Relative Energy (hartree)	Relative Energy (kcal/mol)
(E, trans)-2-butyl-3-(hex-1-enyl)oxirane (**4.7**)	B3LYP 6-311+G(d,p)	-545.5954	0	0
(E, cis)-2-butyl-3-(hex-1-enyl)oxirane (**4.10**)	B3LYP 6-311+G(d,p)	-545.5937	0.001742	1.09
(Z, trans)-2-butyl-3-(hex-1-enyl)oxirane (**4.11**)	B3LYP 6-311+G(d,p)	-545.5928	0.002631	1.65
(Z-cis)-2-butyl-3-(hex-1-enyl)oxirane (**4.8**)	B3LYP 6-311+G(d,p)	-545.5900	0.005477	3.44
Cis-2,5-dibutyl-2,5-dihydrofuran (**4.9**)	B3LYP 6-311+G(d,p)	-545.6172	-0.02175	-13.65
Trans-2,5-dibutyl-2,5-dihydrofuran (**4.12**)	B3LYP 6-311+G(d,p)	-545.6176	-0.02217	-13.91
(E)-dodec-7-en-5-one (**4.13**)	B3LYP 6-311+G(d,p)	-545.6386	-0.04312	-27.06
(Z)-dodec-7-en-5-one (**4.37**)	B3LYP 6-311+G(d,p)	-545.6359	-0.04042	-25.37
(E)-dodec-6-en-5-one (**4.38**)	B3LYP 6-311+G(d,p)	-545.6408	-0.04537	-28.47



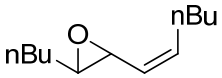
4.7

C	0.00000000	0.00000000	0.00000000
O	0.79798900	1.07275800	-0.51462100
C	1.24526900	-0.28801000	-0.73800400
C	2.49593300	-0.69222400	-0.06714300
C	3.43410400	-1.45004000	-0.63923700
C	4.71502200	-1.88813900	0.00930400
C	5.96728700	-1.41892300	-0.75344700
C	7.27773500	-1.89594200	-0.11786400
C	8.52126100	-1.43495500	-0.88364000
H	8.51625400	-1.81354100	-1.91068800
H	8.57197700	-0.34285300	-0.93475300
H	9.43870300	-1.78770700	-0.40442400
H	7.33028700	-1.53302700	0.91578700
H	7.27141200	-2.99107900	-0.05572300
H	5.96246900	-0.32400600	-0.80927500
H	5.91475600	-1.77798300	-1.78926800
H	4.75028700	-1.52117400	1.04097800
H	4.73329100	-2.98524300	0.06747400
H	3.28085300	-1.78169700	-1.66681000
H	2.62833300	-0.33138300	0.95113400
H	1.14155000	-0.61231900	-1.77301600
C	-1.36842500	-0.19276300	-0.60760700
C	-1.99806300	-1.54475400	-0.24497100
C	-3.39862600	-1.73565700	-0.83771100
C	-4.03181100	-3.08052800	-0.46969800
H	-5.02752800	-3.18612000	-0.90905400
H	-3.42154100	-3.91650200	-0.82595600
H	-4.13510000	-3.18598800	0.61493300
H	-4.04779600	-0.92013700	-0.49699500
H	-3.34315200	-1.64385100	-1.92911000
H	-1.34422100	-2.35569400	-0.58907000
H	-2.05371200	-1.64108400	0.84695700
H	-2.01818900	0.62165900	-0.26351600
H	-1.28916200	-0.08857000	-1.69510000
H	0.04195800	-0.08501300	1.08730000



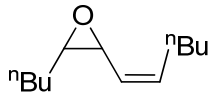
4.10

C	0.00000000	0.00000000	0.00000000
O	-0.90556600	0.87108000	-0.68692300
C	-1.44360500	-0.01139100	0.32862700
C	-2.39199600	-1.05304500	-0.11295700
C	-3.48678500	-1.38367200	0.57652200
C	-4.48404500	-2.43243600	0.17821700
C	-5.90383800	-1.87032500	-0.01888700
C	-6.93785200	-2.94697400	-0.36643800
C	-8.34811600	-2.38481200	-0.56742700
H	-9.06129600	-3.17543500	-0.81653800
H	-8.70812600	-1.88588200	0.33789800
H	-8.36879500	-1.65090500	-1.37911500
H	-6.62111300	-3.47138300	-1.27622000
H	-6.95411400	-3.70142200	0.42955900
H	-6.21641600	-1.34888600	0.89486400
H	-5.88129000	-1.11228400	-0.81051200
H	-4.15183800	-2.92857300	-0.74025200
H	-4.52128000	-3.20741500	0.95628400
H	-3.69923300	-0.85173000	1.50458200
H	-2.17308200	-1.55280400	-1.05269900
H	-1.73904800	0.51070400	1.23823200
C	0.71270300	-1.05978900	-0.80586000
C	1.38438400	-2.11796300	0.08025100
C	2.16565900	-3.16733900	-0.71926200
C	2.84493700	-4.21659500	0.16533300
H	3.39482400	-4.94783700	-0.43344400
H	3.55533700	-3.75118600	0.85588000
H	2.11101100	-4.76352100	0.76564100
H	1.48598700	-3.66522800	-1.42115800
H	2.92081700	-2.66237700	-1.33357800
H	2.06473500	-1.62430500	0.78601900
H	0.62230900	-2.61835900	0.69000000
H	0.01399300	-1.53484000	-1.49956500
H	1.46987600	-0.56188400	-1.42439100
H	0.64237300	0.52513500	0.70988000



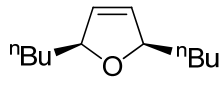
4.11

C	0.00000000	0.00000000	0.00000000
O	-0.85422100	-0.75027600	-0.86899800
C	-1.44278500	0.30905800	-0.07083900
C	-2.38727600	-0.12032700	0.97988800
C	-3.49761700	0.51730500	1.36772700
C	-4.06610100	1.80317400	0.83516700
C	-5.51446200	1.64994500	0.33607400
C	-6.12895700	2.96700500	-0.15052200
C	-7.57064900	2.81370700	-0.64355000
H	-8.22246500	2.43681600	0.15089800
H	-7.97992700	3.76928100	-0.98289400
H	-7.63019300	2.11103500	-1.48052400
H	-5.50950300	3.37822400	-0.95687500
H	-6.09683700	3.70214100	0.66301400
H	-6.13253300	1.23722600	1.14345100
H	-5.53760600	0.91153600	-0.47397800
H	-3.44505900	2.20779200	0.03109400
H	-4.05216200	2.55363400	1.63770700
H	-4.07914300	0.05802500	2.16558600
H	-2.12424300	-1.05663700	1.46593900
H	-1.72131700	1.17811800	-0.66140000
C	1.04845600	0.87614200	-0.64255000
C	1.63995400	1.90247700	0.33289600
C	2.72509700	2.78297100	-0.29804000
C	3.30917500	3.81051600	0.67531600
H	4.07807000	4.42194900	0.19519900
H	2.53366100	4.48604000	1.04994100
H	3.76683600	3.32094000	1.54071500
H	3.52939100	2.14414900	-0.68223100
H	2.30651700	3.30136000	-1.16914100
H	0.83598600	2.54006400	0.72112600
H	2.06050400	1.38047600	1.20190800
H	1.84705000	0.23388400	-1.03433300
H	0.60445100	1.38239100	-1.50641000
H	0.33758500	-0.56805900	0.86848400



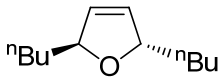
4.8

C	0.00000000	0.00000000	0.00000000
O	0.76169700	1.06079300	0.58406200
C	1.41911600	-0.21291600	0.37303300
C	1.84661200	-0.94079600	1.58606500
C	2.89608200	-1.76485900	1.68858500
C	3.88254900	-2.15754400	0.62434000
C	5.33997400	-1.87607300	1.03213600
C	6.36173800	-2.34512000	-0.00943300
C	7.81065600	-2.06492400	0.39932600
H	8.06173300	-2.57023500	1.33724200
H	8.51427200	-2.41110400	-0.36279300
H	7.98019700	-0.99362800	0.54575000
H	6.15186500	-1.85493000	-0.96796300
H	6.23195500	-3.42043900	-0.18303500
H	5.54718500	-2.36772500	1.99117200
H	5.46154400	-0.80077100	1.20850600
H	3.66499800	-1.65777800	-0.32380100
H	3.77726400	-3.23412500	0.43028100
H	3.07585300	-2.21621700	2.66316200
H	1.24234400	-0.76063700	2.46961800
H	2.13416300	-0.18771600	-0.44537000
C	-1.18275200	-0.54029400	0.76781300
C	-1.66499200	-1.88943000	0.21718900
C	-2.90185300	-2.43221000	0.94240700
C	-3.37889400	-3.77975800	0.39376200
H	-4.26046300	-4.13948000	0.93138600
H	-3.64386400	-3.70438100	-0.66561000
H	-2.59946400	-4.54269800	0.48586400
H	-2.67789300	-2.53165400	2.01134500
H	-3.71392600	-1.69878300	0.86885100
H	-1.89103000	-1.78793400	-0.85221100
H	-0.85087500	-2.62075500	0.28965000
H	-0.92912500	-0.63372500	1.82679000
H	-1.99379800	0.19594600	0.70676000
H	-0.19050400	0.14679300	-1.06518600



4.9

C	0.00000000	0.00000000	0.00000000
C	-0.52378800	-0.29743500	1.38073200
C	-1.85241200	-0.29745200	1.38072100
C	-2.37619100	-0.00002300	-0.00001600
O	-1.18809100	0.24134300	-0.77684500
C	-3.31848600	1.20382400	-0.11029900
C	-4.69865000	0.97116800	0.51491400
C	-5.64154200	2.17024700	0.35769600
C	-7.02448200	1.93626100	0.97244600
H	-7.67282700	2.80684000	0.84017700
H	-7.52294400	1.07813600	0.51047100
H	-6.95200900	1.73688600	2.04644900
H	-5.18112100	3.05250000	0.81826800
H	-5.74963400	2.40538100	-0.70782900
H	-5.16246300	0.08760200	0.05703600
H	-4.59350800	0.74157600	1.58271100
H	-2.83203300	2.07111100	0.34999900
H	-3.43037500	1.43270700	-1.17577900
H	-2.88971100	-0.88329800	-0.41398600
H	-2.49418900	-0.49383300	2.22990100
H	0.11798000	-0.49380400	2.22992000
C	0.94228700	1.20385100	-0.11029400
C	2.32210000	0.97157400	0.51583900
C	3.26563400	2.16993800	0.35702200
C	4.64832900	1.93616700	0.97240600
H	5.29713300	2.80623000	0.83899500
H	4.57553800	1.73840400	2.04668500
H	5.14645400	1.07711800	0.51178900
H	3.37406100	2.40342300	-0.70883100
H	2.80557400	3.05311500	0.81618300
H	2.21640600	0.74382000	1.58397200
H	2.78568200	0.08702500	0.05962300
H	1.05480000	1.43225000	-1.17581400
H	0.45548900	2.07130900	0.34931000
H	0.51353800	-0.88326400	-0.41397100



4.12

C	0.00000000	0.00000000	0.00000000
C	0.85311300	1.18732600	-0.35762300
C	1.98686300	0.79016900	-0.92427300
C	2.04146000	-0.71420300	-0.98748300
O	0.79394800	-1.13375900	-0.40075600
C	3.21278200	-1.36329200	-0.23904100
C	4.57626000	-1.12868200	-0.89893700
C	5.72419600	-1.85353400	-0.18566400
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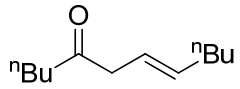

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C	-9.81308400	1.55779200	0.58685500
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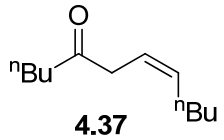

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C	7.48818900	1.74266600	0.11478500
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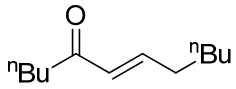

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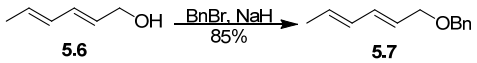
APPENDIX 5

A5.1 Experimental Procedures for Chapter 5

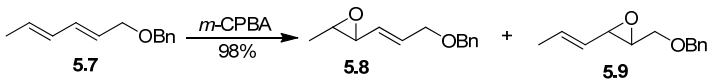
General Information: Commercial reagents were purchased and used without further purification. All glassware was flame dried and reactions were performed under a nitrogen atmosphere, unless otherwise stated. Toluene, benzene, dichloromethane, diethyl ether, and THF were dried over a column of alumina. Flash chromatography was done with Silicycle SiliaFlash® F60 silica, and thin layer chromatography (TLC) was performed with EMD 250 μm silica gel 60-F_{254} plates. ^{1}H and ^{13}C NMR data was acquired on a Varian Inova 400, 500, or 600 (400, 500 or 600 MHz) spectrometer and referenced to residual protic solvent. IR was taken on a Mattson Instruments Research Series FTIR spectrometer. High-resolution mass spectrometry was performed at the University of Illinois at Urbana-Champaign facility.



5.6 **5.7**

Benzyl ether **5.7**. A 1L flask equipped with a stir bar containing DMF (500 mL) and sodium hydride (60% dispersion in mineral oil, 4.49 g, 112.24 mmol) was cooled to 0°C in an ice bath, and then a solution of (2*E*, 4*E*)-2,4-hexadien-1-ol **(5.6)** (10.0 g, 102 mmol) in DMF (10 mL) was slowly added. After 1 hour, sodium iodide (0.49 g, 20.5 mmol) and benzyl chloride (11.8 mL, 13.0 g, 102 mmol) were added. After 2 hours, the reaction was quenched with water and diluted with diethyl ether. The layers were separated, and the aqueous layer was extracted (2x) with diethyl ether. The combined organic portions were then washed with brine, dried over $MgSO_4$, and the solvent was removed *in vacuo*. The crude product was purified by chromatography to give benzyl ether **5.7** as a colorless oil (16.26 g, 85%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.26 (m, 5H), 6.23 (dd, *J* = 15.2, 10.5, 1H), 6.13 – 6.03 (m, 1H), 5.71 – 5.60 (m, 2H), 4.51 (s, 2H), 4.05 (d, *J* = 6.3, 2H), 1.77 (d, *J* = 6.7, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.6, 133.6, 131.0 130.3, 128.6, 128.0, 127.8, 126.8, 72.1, 70.8, 18.3. **IR** (neat) 3062, 3026, 2932, 2910, 2853, 1496, 1453, 1361, 1113, 1073, 990 cm^{-1}. **HRMS** (EI^+) *m/z* 188.1198 [calculated mass for $C_{13}H_{16}O$ (M^+) 188.1201].

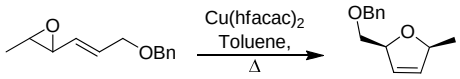


5.7 **5.8** **5.9**

Vinyl oxiranes **5.8** *and* **5.9**: To a 500 mL flask equipped with a stir bar was added methylene chloride (300 mL), (*E*,*E*)-1-benzyloxy-2,4-hexadiene (5.9 g, 31.3 mmol), Na_2HPO_4 (7.73 g, equal mass with *m*-CPBA), and *m*-CPBA (77%, 7.73 g, 34.5 mmol). After 1 hour, the reaction was cooled to 0°C and filtered through celite. It

was then diluted with additional diethyl ether and washed with 1 M NaOH, a saturated $NaHCO_3$ solution (2x), water, and dried over $MgSO_4$. The solvent was removed *in vacuo* to give a clear oil (6.27 g, 98%) that was a 1.5:1 (**5.8**:**5.9**) mixture of regioisomers. The regioisomeric vinyl oxirane products could be separated by column chromatography (10-20% ether : 90-80% pentane). For compound **5** characterization data matched previously reported in the literature.[1]

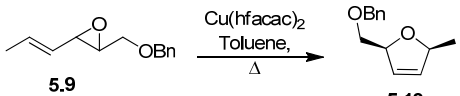
(**5.9**) **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.51 – 7.11 (m, 5H), 6.01 – 5.88 (m, 1H), 5.20 (dddd, *J* = 15.3, 8.3, 3.1, 1.5, 1H), 4.67 – 4.49 (m, 2H), 3.74 (dd, *J* = 11.5, 3.2, 1H), 3.51 (dd, *J* = 11.5, 5.5, 1H), 3.24 (dd, *J* = 8.3, 2.2, 1H), 3.13 – 3.07 (m, 1H), 1.74 (dd, *J* = 6.6, 1.6, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.1, 132.5, 128.6, 128.1, 128.0, 128.0, 73.5, 70.2, 58.8, 56.3, 18.1. **IR** (neat) 3087, 3063, 3029, 2989, 2966, 2938, 2917, 2857, 1496, 1453, 1364, 1239, 1206, 1105, 963, 874, 739, 699 cm^{-1}. **HRMS** (EI^+) *m/z* 204.11496 [calculated mass for $C_{13}H_{16}O_2$ (M^+) 204.11503].



5.8 **5.10**

2,5-Dihydrofuran **5.10** (obtained from **5.9**): To a flame dried 13x100 mm threaded culture tube was added vinyl oxirane **5.9** (25 mg, 0.12 mmol) in dry toluene (1 mL). The culture tube was fitted with a threaded septum cap and then submerged in an oil bath at 150ºC. A syringe pump was used to add toluene over 8 hours (0.5 mL, 0.63 mol%/hour) which contained $Cu(hfacac)_2$ (3.0 mg, 0.0061 mmol, 0.05 equiv.). The solution was heated for a total of 12 hours and then cooled to room temperature. The reaction mixture was filtered through neutral alumina (activity grade 1) washing with ethyl acetate and then purified by flash chromatography on silica gel (10% ether : 90% pentane, $KMnO_4$) to yield of 2,5-dihydrofuran **5.10** (23.5 mg, 94%, 0.12 mmol), (Crude diastereomeric ratio >20:1, purified >20:1 *cis:trans*).

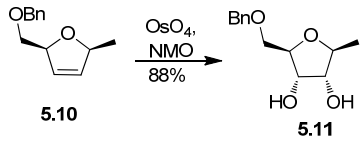
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.00 (m, 5H), 5.85 (d, *J* = 6.0, 1H), 5.78 (d, *J* = 6.0, 1H), 4.99 – 4.90 (m, 2H), 4.66 – 4.54 (m, 2H), 3.54 – 3.47 (m, 2H), 1.29 (d, *J* = 6.3, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.5, 133.1, 128.5, 127.8, 127.7, 127.1, 85.5, 82.5, 74.1, 73.6, 23.0. **IR** (neat) 3312, 3089, 3064, 3031, 2971, 2924, 2859, 1453, 1366, 1094 cm^{-1}. **HRMS** (EI^+) *m/z* 202.0996 [calculated mass for $C_{13}H_{14}O_2$ ($M-H_2^+$) 202.0994].



5.9 **5.10**

2,5-Dihydrofuran **5.10** (obtained from **5.9**): To a flame dried 13x100 mm threaded culture tube was added vinyl oxirane **5.9** (25 mg, 0.12 mmol) in dry toluene (1 mL). The culture tube was fitted with a threaded septum cap and then submerged in an oil bath at 150ºC. A syringe pump was used to add toluene over 8 hours (0.5 mL, 0.63 mol%/hour) which contained $Cu(hfacac)_2$ (3.0 mg, 0.0061 mmol, 0.05 equiv.). The solution was heated for a total of 12 hours and then cooled to room temperature. The reaction mixture was filtered through neutral alumina (activity grade 1) washing with ethyl acetate and then purified by flash chromatography on silica gel (10% ether : 90% pentane, $KMnO_4$) to yield of 2,5-dihydrofuran **5.10** (22.0 mg, 88%, 0.11 mmol), (Crude diastereomeric ratio 13:1, purified >20:1 *cis:trans*).

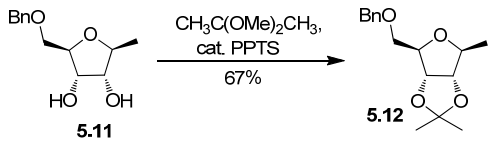
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 – 7.00 (m, 5H), 5.85 (d, *J* = 6.0, 1H), 5.78 (d, *J* = 6.0, 1H), 4.99 – 4.90 (m, 2H), 4.66 – 4.54 (m, 2H), 3.54 – 3.47 (m, 2H), 1.29 (d, *J* = 6.3, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.5, 133.1, 128.5, 127.8, 127.7, 127.1, 85.5, 82.5, 74.1, 73.6, 23.0. **IR** (neat) 3312, 3089, 3064, 3031, 2971, 2924, 2859, 1453, 1366, 1094 cm^{-1}. **HRMS** (EI$^+$) *m/z* 202.0996 [calculated mass for $C_{13}H_{14}O_2$ (M-H_2^+) 202.0994].



5.10 **5.11**

Diol **5.11**: To a stirred flask containing acetone (5.6 mL), water (5.6 mL), dihydrofuran **5.10** (1.00 g, 4.93 mmol), and 4-methylmorpholine *N*-oxide (1.01 g, 8.63 mmol) was added OsO_4 (2.5% in *t*BuOH, 0.25 mL). After 24 hours, the reaction was quenched with a solution of sodium bisulfite and diluted with ethyl acetate. The layers were separated, and the aqueous layer was extracted with ethyl acetate (3x). The combined organic portions were dried over Na_2SO_4. The solvent was removed *in vacuo* and was purified by chromatography (30-70% ethyl acetate : 70-30 % hexanes) to give diol **5.11** (1.03 g, 88%).

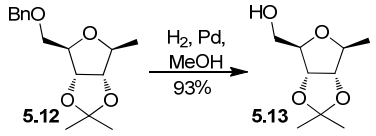
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.26 (m, 5H), 4.56 (d, *J* = 1.1, 2H), 3.96 (t, *J* = 5.5, 1H), 3.91 (q, *J* = 4.8, 1H), 3.81 (ap, *J* = 6.2, 1H), 3.66 (ddd, *J* = 14.4, 8.5, 4.6, 1H), 3.59 (dd, *J* = 4.7, 0.9, 2H), 3.15 (bs, 1H), 3.04 (bs, 1H), 1.28 (d, *J* = 6.3, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.1, 128.6, 127.9(7), 127.9(6), 82.8, 79.6, 76.4, 73.8, 72.8, 71.0, 19.0. **IR** (neat) 3388, 2906, 1496, 1452, 1094, 1019, 738, 696 cm^{-1}. **HRMS** (ESI) *m/z* 239.1275 [calculated mass for $C_{13}H_{19}O_4$ (M^+) 239.1283].



5.11 **5.12**

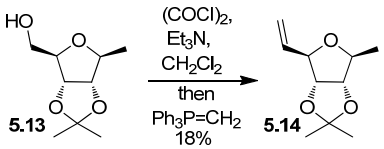
Acetonide **5.12**: To a 100 mL flask equipped with a stir bar was added methylene chloride (40 mL), diol **5.11** (1.03 g, 4.32 mmol), pyridinium *p*-toluenesulfonate (0.22 g, 0.86 mmol), and 2,2-dimethoxypropane (4.5 g, 43.2 mmol). The reaction was left to stir for 3 hours. It was diluted with methylene chloride and washed with $NaHCO_3$ and brine. The solution was dried over Na_2SO_4 and purified by chromatography (10-30% ether : 90-70% pentane) to give acetonide **5.12** (0.88 g, 67%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.26 (m, 5H), 4.59 (s, 2H), 4.55 (dd, *J* = 6.96, 4.47, 1H), 4.25 (dd, *J* = 6.94, 5.05, 1H), 4.06 (dd, *J* = 9.55, 4.40, 1H), 4.03 – 3.91 (m, 1H), 3.64 – 3.52 (m, 2H), 1.53 (s, 3H), 1.33 (s, 3H), 1.31 (d, *J* = 6.3, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 138.2, 128.6, 128.0, 127.9, 114.9, 86.2, 83.2, 82.6, 80.9, 73.8, 70.7, 27.6, 25.7, 19.2. **IR** (neat) 3088, 3062, 3031, 2982, 2932, 2870, 1497, 1454, 1372, 1253, 1240, 1211, 1158, 1118, 1076 cm^{-1}. **HRMS** (EI$^+$) *m/z* 278.1515 [calculated mass for $C_{16}H_{22}O_4$ (M^+) 278.1518].



Primary alcohol **5.13**: To a 50 mL flask equipped with a stir bar was added methanol (25 mL), acetonide **5.12** (0.80 g, 2.87 mmol), and 10% Pd/C (0.029 g). A balloon of hydrogen gas was then added. After 18 hours, the reaction was filtered through celite with ethyl acetate. The solvent was removed *in vacuo* to afford primary alcohol **5.13** (0.50 g, 93%).

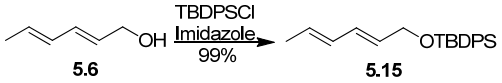
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.61 (dd, *J* = 6.99, 4.51, 1H), 4.23 (dd, *J* = 6.96, 5.23, 1H), 4.12 – 3.88 (m, 2H), 3.82 (ddd, *J* = 11.93, 4.90, 3.37, 1H), 3.67 (ddd, *J* = 12.00, 7.63, 4.45, 1H), 2.00 (dd, *J* = 7.62, 5.03, 1H), 1.53 (s, 3H), 1.33 (s, 3H), 1.31 (d, *J* = 6.35, 3H). **^{13}C NMR** (125 MHz, $CDCl_3$) δ 115.0, 86.3, 84.3, 81.8, 80.7, 63.0, 27.6, 25.6, 19.1. **IR** (neat) 3466, 2982, 2934, 2878, 1456, 1382, 1263, 1241, 1212, 1158, 1122, 1076 cm^{-1}. **HRMS** (EI$^+$) *m/z* 189.1123 [calculated mass for $C_9H_{17}O_4$ ($M+H^+$) 189.1127].



Vinyl Tetrahydrofuran **5.14**. Stock solutions of all reagents were prepared. To a 5 mL flask equipped with a stir bar was added CH_2Cl_2 (1 mL) and a solution of oxalyl chloride (0.0210g, 0.166 mmol). The solution was cooled to -78°C and DMSO was

added (0.0259 g, 0.332 mmol). After 15 minutes, primary alcohol **5.13** (0.0260 g, 0.138 mmol) was added, and the reaction was left to stir for 40 minutes at -78°C. After 40 minutes, triethyl amine was added (0.0699 g, 0.691 mmol), and after an additional 20 minutes, the reaction was warmed to 0°C in an ice bath. After 30 minutes, the reaction was filtered through a plug of celite with 50% diethyl ether/pentane. The solvent was removed *in vacuo*, 0.5 mL of diethyl ether was added, and the solution was cooled to 0°C. In the meantime, methyl triphenylphosphonium bromide (0.247 g, 0.691 mmol) was added to a 10 mL flask containing diethyl ether (3.5 mL), cooled to 0°C, and equipped with a stir bar. Potassium *t*-butoxide (0.0814 g, 0.725 mmol) was added to the solution. After 1 hour, 1.5 mL of this solution (2 eq) was added to the crude aldehyde solution. Upon completion, the reaction was quenched with ammonium chloride and diluted with diethyl ether. The layers were separated, and the organic layer was washed with saturated NaCl and dried over $MgSO_4$. The solvent was removed *in vacuo*. The product was purified by chromatography (5% ethyl acetate : 95% hexanes) to give vinyl tetrahydrofuran **5.14** (0.0047 g, 18%). The NMR data matched that previously published in the literature.[2]

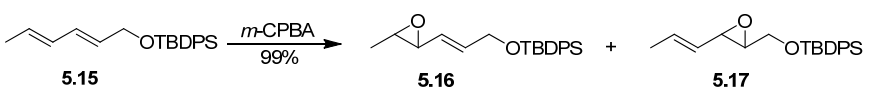
^{1}H NMR (600 MHz, $CDCl_3$) δ 5.90 (ddd, *J* = 17.08, 10.50, 6.43, 1H), 5.39 (td, *J* = 17.23, 1.35, 1H), 5.23 (td, *J* = 10.50, 1.28, 1H), 4.45 (dd, *J* = 6.99, 4.95, 1H), 4.28 (ddd, *J* = 17.44, 6.60, 4.89, 2H), 4.07 – 3.89 (m, 1H), 1.55 (s, 3H), 1.34 (s, 3H), 1.33 (d, *J* = 6.41, 3H).



5.6 **5.15**

Silyl Ether **5.15**: To a 250 mL flask was added 2,4-hexadien-1-ol (3.4 g, 34.6 mmol, 1 equiv.) and CH_2Cl_2 (100 mL). A stir bar was added followed by imidazole (4.2 g, 61.7 mmol, 1.8 equiv.). Lastly, *tert*-butylchlorodiphenylsilane (12.6 g, 45.8 mmol, 1.3 equiv.) was added and the reaction was stirred for 10 hours at room temperature. The reaction was diluted with diethyl ether and washed with 1 M HCl. The solvent was removed *in vacuo* and then purified by column chromatography (2.5% ether: 97.5% pentane, anisaldehyde) to yield 11.5 g of product (34.2 mmol, 99%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.74 (m, 4H), 7.55 – 7.38 (m, 6H), 6.33 (dd, *J* = 15.0, 10.7, 1H), 6.23 – 6.06 (m, 1H), 5.83 – 5.66 (m, 2H), 4.32 (d, *J* = 3.8, 2H), 1.83 (d, *J* = 6.6, 3H), 1.16 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.7, 133.9, 131.3, 130.4, 129.8, 129.6, 129.1, 127.8, 64.5, 27.0, 19.5, 18.3. **IR** (neat) 3023, 2932, 1959, 1824, 1472, 1427, 1380, 1112, 1050, 988, 823, 702, 606, 491 cm^{-1}. **HRMS** (EI^+) *m/z* 336.19001 [calculated mass for $C_{22}H_{28}OSi$ (M^+) 336.19095].

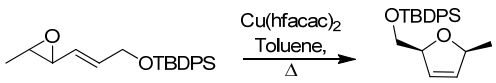


5.15 **5.16** **5.17**

Vinyl Oxiranes **5.16** and **5.17**: To a 500 mL flask equipped with a stir bar was added methylene chloride (320 mL), silyl ether **5.15** (12.2 g, 36.3 mmol), Na_2HPO_4 (9.81 g, equal mass with m-CPBA), and m-CPBA (70%, 9.81 g, 39.8 mmol, 1.1 equiv.). After 1 hour, the reaction was cooled to 0°C and filtered through celite washing with diethyl ether. It was then diluted with additional diethyl ether and washed with 1 M NaOH, a saturated $NaHCO_3$ solution, water, and dried over $MgSO_4$. The solvent was removed *in vacuo* to give a clear oil that was purified by column chromatography (2.5% ether: 97.5 % pentane, anisaldehyde). The regioisomeric vinyl oxirane products are readily separable and yielded 7.2 g of **5.16** and 5.5 g of **5.17 (**1.3:1 ratio, 36.0 mmol, 99%).

Vinyl Oxirane **5.16. ^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.69 – 7.64 (m, 4H), 7.43 – 7.33 (m, 6H), 5.97 (ddd, *J* = 15.5, 4.6, 4.1, 1H), 5.54 (ddt, *J* = 15.4, 7.9, 1.9, 1H), 4.21 (dd, *J* = 4.3, 1.8, 2H), 3.08 (dd, *J* = 7.9, 2.1, 1H), 2.89 (qd, *J* = 5.2, 2.2, 1H), 1.33 (d, *J* = 5.2, 3H), 1.06 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.6, 135.6, 134.1, 133.6, 133.5, 129.9, 127.9, 127.3, 63.7, 59.3, 56.6, 27.0, 19.4, 17.8. **IR** (neat) 2960, 2857, 1428, 1112, 963, 823, 703, 491 cm^{-1}. **HRMS** (EI^+) *m/z* 295.11565 [calculated mass for $C_{18}H_{19}O_2Si$ (M-*t*Bu^+) 295.11544].

Vinyl Oxirane **5.17**. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.77 – 7.63 (m, 4H), 7.49 – 7.29 (m, 6H), 5.98 – 5.82 (m, 1H), 5.20 (ddq, *J* = 15.3, 8.2, 1.6, 1H), 3.83 (dd, *J* = 11.8, 3.5, 1H), 3.75 (dd, *J* = 11.8, 4.5, 1H), 3.21 (dd, *J* = 8.2, 2.1, 1H), 3.04 (ddd, *J* = 4.5, 3.5, 2.2, 1H), 1.72 (dd, *J* = 6.6, 1.6, 3H), 1.06 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.8, 135.7, 133.4(4), 133.3(8), 132.0, 129.9, 128.3, 127.9(0), 127.8(9), 64.0, 60.1, 56.4, 26.9, 19.4, 18.1. **HRMS** (EI^+) *m/z* 295.11522 [calculated mass for $C_{18}H_{19}O_2Si$ (M-*t*Bu^+) 295.11544].

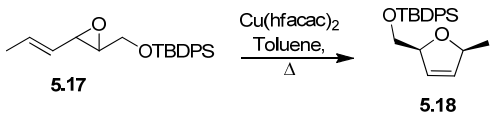


5.16 **5.18**

2,5-Dihydrofuran **5.18** from **5.16**: To a flame dried 13x100 mm threaded culture tube was added vinyl oxirane **5.16** (25 mg, 0.071 mmol) in dry toluene (0.6 mL). The culture tube was fitted with a threaded septum cap and then submerged in an oil bath at 150ºC. A syringe pump was used to add toluene over 10 hours (0.1 mL, 0.50 mol%/hour) which contained $Cu(hfacac)_2$ (1.76 mg, 0.0035 mmol, 0.05 equiv.). The solution was heated for a total of 12 hours and then cooled to room temperature. The reaction mixture was filtered through neutral alumina (activity grade 1) washing with ethyl acetate and then purified by flash chromatography on silica gel (2.5% ether : 97.5% pentane, anisaldehyde) to yield of 2,5-dihydrofuran **5.18** (21 mg, 84%, 0.060 mmol), (Crude diastereomeric ratio >20:1, purified >20:1 *cis:trans*).

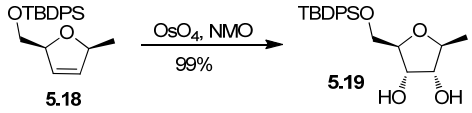
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.66 (m, 4H), 7.45 – 7.32 (m, 6H), 5.82 (s, 2H), 4.98 – 4.89 (m, 1H), 4.89 – 4.83 (m, 1H), 3.71 (dd, *J* = 10.3, 4.9, 1H), 3.63 (dd, *J* = 10.3, 5.4, 1H), 1.25 (d, *J* = 6.4, 3H), 1.05 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.9, 135.8, 133.9, 133.7, 132.7, 129.8(2), 129.7(8), 127.8, 127.5, 87.0, 82.5, 77.6,

77.2, 76.9, 67.7, 27.0, 23.0, 19.5. **IR** (neat) 2922, 2854, 1783, 1532, 1450, 1426, 1363, 1112, 1091, 912, 741, 701 cm^{-1}. **HRMS** (EI^+) *m/z* 295.11644 [calculated mass for $C_{18}H_{19}O_2Si$ (M-*t*Bu^+) 295.11544].



2,5-Dihydrofuran **5.18** from **5.17**: To a flame dried 13x100 mm threaded culture tube was added vinyl oxirane **5.17** (25 mg, 0.071 mmol) in dry toluene (0.6 mL). The culture tube was fitted with a threaded septum cap and then submerged in an oil bath at 150ºC. A syringe pump was used to add toluene over 10 hours (0.1 mL, 0.50 mol%/hour) which contained $Cu(hfacac)_2$ (1.76 mg, 0.0035 mmol, 0.05 equiv.). The solution was heated for a total of 12 hours and then cooled to room temperature. The reaction mixture was filtered through neutral alumina (activity grade 1) washing with ethyl acetate and then purified by flash chromatography on silica gel (2.5% ether : 97.5% pentane, anisaldehyde) to yield 2,5-dihydrofuran **5.18** (20 mg, 80%, 0.057 mmol), (Crude diastereomeric ratio >20:1, purified >20:1 *cis:trans*).

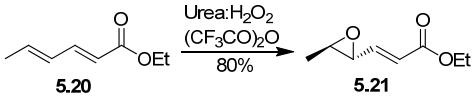
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 – 7.66 (m, 4H), 7.45 – 7.32 (m, 6H), 5.82 (s, 2H), 4.98 – 4.89 (m, 1H), 4.89 – 4.83 (m, 1H), 3.71 (dd, *J* = 10.3, 4.9, 1H), 3.63 (dd, *J* = 10.3, 5.4, 1H), 1.25 (d, *J* = 6.4, 3H), 1.05 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.9, 135.8, 133.9, 133.7, 132.7, 129.8(2), 129.7(8), 127.8, 127.5, 87.0, 82.5, 77.6, 77.2, 76.9, 67.7, 27.0, 23.0, 19.5. **IR** (neat) 2922, 2854, 1783, 1532, 1450, 1426, 1363, 1112, 1091, 912, 741, 701 cm^{-1}. **HRMS** (EI^+) *m/z* 295.11644 [calculated mass for $C_{18}H_{19}O_2Si$ (M-*t*Bu^+) 295.11544].



Diol **5.19**: To a stirred flask containing acetone (4.5 mL), water (4.5 mL), dihydrofuran **5.18** (0.31 g, 0.88 mmol), and 4-methylmorpholine *N*-oxide (0.31 g, 2.64 mmol, 3 equiv.) was added OsO_4 (2.5% in *t*BuOH, 1.0 mL, 0.1 equiv.). After 12 hours, the reaction was quenched with a solution of sodium bisulfite and diluted with ethyl acetate. The reaction was stirred vigorously for 16 hours and then the layers were separated. The aqueous layer was extracted with ethyl acetate three additional times. The combined organic portions were dried over Na_2SO_4. The solvent was removed *in vacuo* and purified by chromatography (60% ether : 40% pentane, anisaldehyde) to yield diol **5.19** (0.34 g 0.88 mmol, 99% yield).

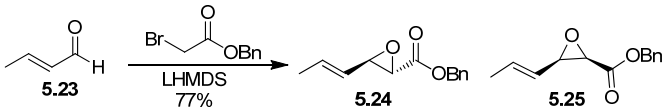
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.60 (m, 4H), 7.53 – 7.30 (m, 6H), 4.20 (bs, 1H), 3.97 – 3.81 (m, 2H), 3.81 – 3.69 (m, 3H), 2.70 (bd, *J* = 5.4, 1H), 2.63 (bd, *J* = 3.1, 1H), 1.31 (d, *J* = 6.2, 3H), 1.05 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.8(4),

135.7(7), 133.4, 133.2, 130.0(2), 129.9(7), 127.9(7), 127.9(3), 84.2, 79.1, 76.9, 72.8, 64.5, 27.0, 19.4, 18.9. **IR** (neat) 3404, 2931, 2858, 1472, 1427, 1112, 1008, 938, 823, 702, 504 cm^{-1}. **HRMS** (ESI) *m/z* 409.1805 [calculated mass for $C_{22}H_{30}O_4NaSi$ ($M+Na^+$) 409.1811].



5.20 **5.21**

Vinyl Oxirane **5.21**: To a 250 mL flask was added ethyl sorbate (1.0 g, 7.1 mmol, 1 equiv.) and CH_2Cl_2 (50 mL). The solution was cooled to 0°C and then (6.7 g, 71.1 mmol, 10 equiv.) H_2O_2:Urea was added. Next, Na_2HPO_4 (9.1 g, 64 mmol, 9 equiv.) was added followed by a slow addition of trifluoroacetic anhydride (2.5 mL, 3.75 g, 17.9 mmol, 2.5 equiv.) The solution was vigorously stirred at 0°C for 4 hours. The reaction was decanted from the solid that aggregates during the course of the reaction. The solid was washed with CH_2Cl_2 and the organic washings are quenched with sat. $NaHCO_3$. The organic layer was dried with Na_2SO_4 and the solvent removed *in vacuo*. The product was clean enough for further reaction but can be purified by silica gel chromatography (20% ether: 80% pentane) to yield epoxide that was slightly volatile (0.88 g, 5.6 mmol, 80%). The product matched existing characterization data.[3]

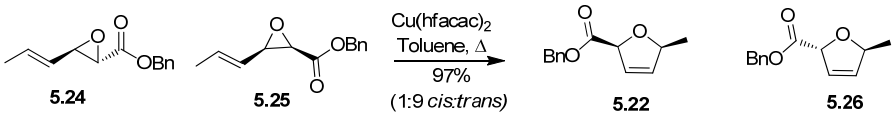


5.23 **5.24** **5.25**

Vinyl Oxiranes **5.24** and **5.25**: To a tall threaded culture tube was added a stir bar, dry THF (1 mL), and LiHMDS (1.24 mL, 1.0 M in THF, 1.24 mmol, 1.02 equiv.) The reaction was cooled to -78°C and a solution of benzyl-2-bromoacetate (0.19 mL, 278 mg, 1.2 mmol, 1 equiv.) in THF (0.5 mL) was added. The solution was stirred for 30 minutes at -78°C and then crotonaldehyde (0.10 mL, 0.085 g, 1.2 mmol, 1 equiv.) was added. The solution was stirred for 1 hour at -78°C and then the cooling bath was removed for 15 minutes before it was quenched with sat. NH_4Cl. The reaction was extracted with CH_2Cl_2 and dried with Na_2SO_4. The product was purified by silica gel chromatography (10% ether : 90% pentane, anisaldehyde) to yield of a 1.2:1 mixture of diasteriomers (**5.25** *cis* : **5.24** *trans*), (204 mg, 0.94 mmol, 77%). The products are separable by column chromatography to yield 60 mg of **5.24** and 132 mg of **5.25**.

Vinyl Oxirane **5.24** **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.40 – 7.31 (m, 5H), 6.03 (dq, *J* = 15.4, 6.6, 1H), 5.34 – 5.08 (m, 3H), 3.56 (dd, *J* = 8.2, 1.8, 1H), 3.40 (d, *J* = 1.9, 1H), 1.75 (dd, *J* = 6.6, 1.7, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.8, 135.2, 134.5, 128.8, 128.7(4), 128.6(5), 126.3, 67.4, 58.4, 54.8, 18.1. **IR** (neat) 3032, 2962, 1748, 1763, 1454, 1424, 1278, 1186, 962, 763 cm^{-1}. **HRMS** (EI^+) *m/z* 218.09465 [calculated mass for $C_{13}H_{14}O_3$ (M^+) 218.09430].

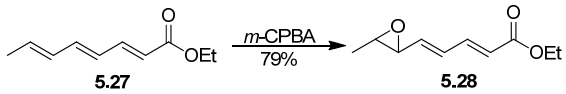
Vinyl Oxirane **5.25** **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.44 – 7.30 (m, 5H), 6.07 (dq, *J* = 15.5, 6.6, 1H), 5.37 (ddq, *J* = 15.5, 8.8, 1.7, 1H), 5.29 (d, *J* = 12.1, 1H), 5.19 (d, *J* = 12.2, 1H), 3.70 (d, *J* = 4.5, 1H), 3.60 (dd, *J* = 8.8, 4.5, 1H), 1.72 (dd, *J* = 6.6, 1.7, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 168.1, 136.1, 135.4, 128.8(4), 128.7(8), 128.7(5), 123.6, 67.36, 58.0, 54.5, 18.3. **IR** (neat) 3053, 2970, 1750, 1497, 1454, 1283, 1186, 967, 746, 698 cm^{-1}. **HRMS** (EI^+) *m/z* 218.09416 [calculated mass for $C_{13}H_{14}O_3$ (M^+) 218.09430].



5.24 **5.25** **5.22** **5.26**

2,5-Dihydrofuran **5.26** (*trans*): To a flame dried 13x100 mm threaded culture tube was added vinyl oxiranes **5.24** and **5.25** (100 mg, 1:1.2, 0.45 mmol) in dry toluene (4.5 mL). Then, $Cu(hfacac)_2$ (23 mg, 0.046 mmol, 0.1 equiv.) was added. The culture tube was fitted with a teflon cap and submerged in an oil bath at 150ºC. After 2 hours the reaction was concentrated and silica gel chromatography was performed (10% ether : 90% pentane, anisaldehyde) to yield **5.26** (97 mg, 0.44 mmol, 97%, crude diastereomeric ratio 1:9, purified 1:9 *cis:trans*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 – 7.28 (m, 5H), 5.97 – 5.90 (m, 1H), 5.84 (dt, *J* = 6.0, 2.1, 1H), 5.34 (dt, *J* = 5.7, 2.1, 1H), 5.24 – 5.14 (m, 3H), 1.31 (d, *J* = 6.4, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.3, 135.7, 134.4, 128.7, 128.4, 128.3, 124.4, 84.1, 83.7, 66.8, 21.5. **IR** (neat) 2972, 2875, 1752, 1455, 1372, 1347, 1314, 1180, 1104, 1015, 745, 695 cm^{-1}. **HRMS** (EI^+) *m/z* 216.07782 [calculated mass for $C_{13}H_{12}O_3$ ($M\text{-}H_2^+$) 216.07865].

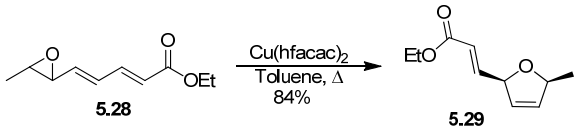


5.27 **5.28**

Vinyl Oxirane **5.28**: To a 200 mL flame dried flask with magnetic stir bar was added methylene chloride (120 mL). To this solution was added (*2E,4E,6E*)-ethyl octa-2,4,6-trienoate[4] (2.00 g, 12.0 mmol, 1 equiv.). Next, was added Na_2HPO_4 (2.7 g) followed by *m*-CPBA (2.7 g, 15.6 mmol, 1.3 equiv.). The solution was stirred at room temperature until the starting material was consumed. The solution was cooled to 0^{o}C and then filtered through celite. The organic filtrate was washed 3 times with sat. $NaHCO_3$ and once with H_2O. The solution was dried with Na_2SO_4 and the solvent removed *in vacuo.* The product was purified by silica gel chromatography (15% ether : 85% pentane) to yield vinyl oxirane **5.28** (1.73 g, 79%).

^{1}H NMR (500 MHz, C_6D_6) δ 7.36 (ddd, *J* = 15.4, 11.2, 0.7, 1H), 6.07 (dd, *J* = 15.3, 11.2, 1H), 5.87 (dd, *J* = 15.4, 0.6, 1H), 5.34 (dd, *J* = 15.3, 7.5, 1H), 4.05 (q, *J* = 7.1, 2H), 2.62 (dd, *J* = 7.5, 1.8, 1H), 2.42 (qd, *J* = 5.1, 2.0, 1H), 0.99 (t, *J* = 7.1, 3H), 0.94

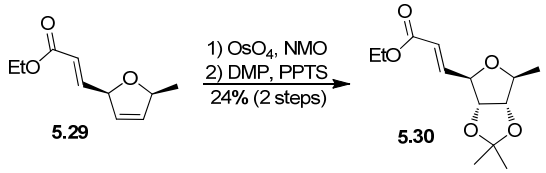
(d, J = 5.1, 3H). **^{13}C NMR** (126 MHz, C_6D_6) δ 166.8, 143.5, 140.1, 131.1, 122.7, 60.6, 58.4, 57.1, 17.8, 14.7. **IR** (neat) 2984, 2932, 1713, 1644, 1619, 1305, 1231, 1145, 1000, 853 cm^{-1}. **HRMS** (EI$^+$) *m/z* 182.0941 [calculated mass for $C_{10}H_{14}O_3$ (M^+) 182.0943]



5.28 **5.29**

2,5-Dihydrofuran **5.29**: To a flame dried 13x100 mm threaded culture tube was added vinyl oxirane **5.28** (25 mg, 0.14 mmol) in dry toluene (1 mL). The culture tube was fitted with a threaded septum cap and then submerged in an oil bath at 150ºC. A syringe pump was used to add toluene over 17 hours (0.5 mL, 0.12 mol%/hour) which contained $Cu(hfacac)_2$ (1.4 mg, 0.0027 mmol, 0.02 equiv.). The solution was heated for a total of 24 hours and then cooled to room temperature. The reaction mixture was filtered through neutral alumina (activity grade 1) washing with ethyl acetate and then purified by flash chromatography on silica gel (20% ether : 80% pentane, $KMnO_4$) to yield of 2,5-dihydrofuran **5.29** (21.0 mg, 84%, 0.12 mmol), (Crude diastereomeric ratio 8:1, purified >20:1 *cis:trans*).

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.83 (dd, J = 15.6, 5.3, 1H), 5.98 (d, J = 15.5, 1H), 5.80 – 5.77 (m, 1H), 5.66 (d, J = 6.0, 1H), 5.31 – 5.22 (m, 1H), 4.98 – 4.89 (m, 1H), 4.13 (q, J = 7.2, 2H), 1.25 (d, J = 6.4, 3H), 1.22 (t, J = 7.2, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.7, 147.9, 132.6, 127.1, 120.7, 85.0, 83.1, 60.7, 22.9, 14.5. **IR** neat 2981, 2954, 2873, 1721, 1657, 1596, 1448, 1370, 1303, 1275, 1180, 1039, 981, 841 cm^{-1}. **HRMS** (EI$^+$) *m/z* 182.09420 [calculated mass for $C_{10}H_{14}O_3$ ($M+H^+$) 182.09430].



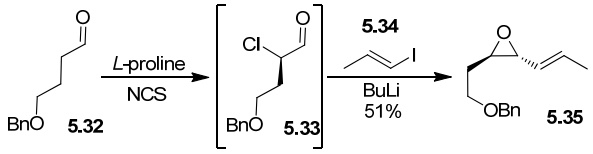
5.29 **5.30**

Acetonide **5.30**: To a stirred flask containing acetone (0.5 mL), water (0.5 mL), dihydrofuran **5.29** (0.014 g, 0.077 mmol), and 4-methylmorpholine *N*-oxide (9 mg, 0.077 mmol, 1 equiv.) was added OsO_4 (2.5% in *t*BuOH, 0.01 mL, cat.). After 24 hours, the reaction was quenched with a solution of sodium bisulfite and diluted with ethyl acetate. The reaction was stirred vigorously for several hours and then the layers were then separated. The aqueous layer was extracted with ethyl acetate three additional times. The combined organic portions were dried over Na_2SO_4. The solvent was removed *in vacuo* and the diol was purified by chromatography (70% ether : 30% pentane, $KMnO_4$), (9.5 mg, 0.043 mmol, 57%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (dd, *J* = 15.7, 4.8, 1H), 6.09 (dd, *J* = 15.6, 1.7, 1H), 4.34 – 4.22 (m, 2H), 4.17 (q, *J* = 7.1, 2H), 3.94 – 3.88 (m, 1H), 3.72 (at, *J* = 5.2, 1H). 2.68 (bd, *J* = 5.8, 1H), 2.47 (bd, *J* = 5.5, 1H), 1.30 (d, *J* = 6.3, 3H), 1.26 (t, *J* = 7.1, 3H).

The diol was prone to epimerization and retro Aldol reactions and therefore it was protected immediately after purification. To a 4 mL reaction vial equipped with a stir bar was added the diol (34 mg, 0.16 mmol), methylene chloride (0.5 mL), pyridinium p-toluenesulfonate (0.01 g, 0.04 mmol, 0.25 equiv.), and 2,2-dimethoxypropane (0.5 mL). The reaction was stirred for 12 hours. It was diluted with methylene chloride and washed with $NaHCO_3$ and brine. The solution was dried over Na_2SO_4 and purified by chromatography (30% ether : 70% pentane, $KMnO_4$) to give acetonide **5.30** (0.017 g, 0.066 mmol, 42% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (dd, *J* = 15.7, 5.0, 1H), 6.11 (dd, *J* = 15.7, 1.7, 1H), 4.49 (dd, *J* = 6.8, 4.9, 1H), 4.44 (td, *J* = 4.9, 1.7, 1H), 4.31 (dd, *J* = 6.8, 4.4, 1H), 4.20 (q, *J* = 6.5, 2H), 4.07 (qd, *J* = 6.4, 4.5, 1H), 1.55 (s, 3H), 1.33 (s, 3H), 1.33 (d, *J* = 6.5, 3H), 1.29 (t, *J* = 7.1, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 166.3, 144.9, 122.2, 115.3, 86.3, 85.1, 83.2, 80.9, 60.7, 27.6, 25.7, 19.3, 14.4. **HRMS** (EI^+) *m/z* 256.1302 [calculated mass for $C_{13}H_{20}O_5$ (M^+) 256.1311].



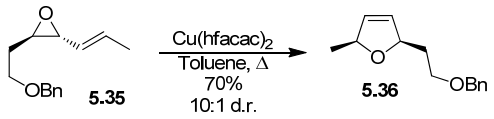
Vinyl Oxirane **5.35**: To a 10 mL flask with a magnetic stir bar was added *L*-Proline (13 mg, 0.11mmol, 0.2 equiv.) followed by aldehyde **5.32** (0.1 g, 0.56 mmol, 1 equiv.) in 1 mL of CH_2Cl_2. The solution was cooled to 0°C and after 15 minutes N-chlorosuccinimide (0.097 g, 0.73 mmol, 1.3 equiv.) was added. The solution was stirred for 2 hours at 0°C and then 1 hour at room temperature, at which point it was quenched by the addition of pentane (5 mL) and filtered through a sintered glass funnel. The solvent was removed *in vacuo* and then resulting crude dissolved in pentane, filtered, and dried with Na_2SO_4. The solvent was removed once again to yield labile aldehyde **5.33**.

^{1}H NMR (400 MHz, $CDCl_3$) δ 9.53 (d, *J* = 1.9, 1H), 7.40 – 7.28 (m, 5H), 4.50 (s, 2H), 4.45 (ddd, *J* = 7.3, 5.3, 1.9, 1H), 3.75 – 3.58 (m, 2H), 2.37 – 2.28 (m, 1H), 2.13 (dddd, *J* = 14.8, 7.5, 6.1, 4.3, 1H), 1.35 – 1.20 (m, 2H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 195.2, 138.0, 128.7, 128.0, 127.9, 73.4, 65.4, 61.7, 33.1.

Aldehyde **5.33** was used without further purification. To another 10 mL round bottom flask was added THF (5 mL) and *E*-1-iodopropene (94 mg, 0.56 mmol, 1 equiv.). The solution was cooled to -78°C and then n-butyl-lithium (0.35 mL, 1.6 M in hexanes, 0.56 mmol, 1 equiv.) was added drop wise. The solution was stirred for 10 minutes at -

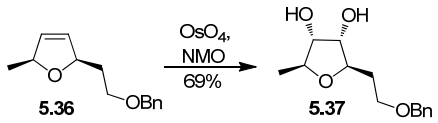
78°C and then aldehyde **5.33** dissolved in THF (0.1 mL) was added. The solution was stirred for 15 minutes at -78°C and then quenched with saturated NH_4Cl and diethyl ether. The solution was warmed to room temperature over 3 hours. The solution was extracted with diethyl ether three times and then dried with Na_2SO_4. The solvent was removed to yield a mixture of epoxide and chloro-alcohol. This crude mixture was dissolved in absolute ethanol (5.6 mL). Then KOH (94 mg, 1.68 mmol, 3 equiv.) was added and the solution was stirred for 30 minutes. The solution was quenched with brine and extracted with pentane. The organic layer was dried with Na_2SO_4 and the solvent removed. The epoxide was purified using silica gel chromatography (20% ether : 80% pentane, anisaldehyde) to yield vinyl oxirane **5.35** (62 mg, 0.28 mmol, 51%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.39 – 7.23 (m, 5H), 5.97 – 5.85 (m, 1H), 5.19 (ddd, *J* = 15.4, 8.2, 1.7, 1H), 4.51 (s, 2H), 3.60 (dd, *J* = 6.7, 5.8, 2H), 3.12 (dd, *J* = 8.2, 2.2, 1H), 2.97 (ddd, *J* = 6.8, 4.8, 2.2, 1H), 1.93 (dtd, *J* = 11.7, 6.7, 4.8, 1H), 1.80 (ddd, *J* = 11.9, 7.2, 4.0, 1H), 1.73 (dd, *J* = 6.6, 1.7, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 138.4, 131.7, 128.8, 128.5, 127.7, 127.7, 73.2, 67.0, 58.8, 58.0, 32.7, 18.1. **IR** (neat) 2918, 2857, 1496, 1463, 1362, 1207, 1099, 963, 879, 734, 698 cm^{-1}. **HRMS** (EI^+) *m/z* 218.13117 [calculated mass for $C_{14}H_{18}O_2$ (M^+) 218.13068].



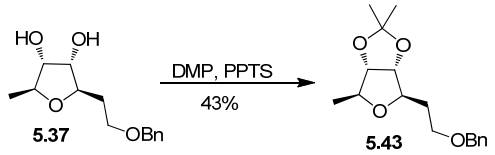
2,5-Dihydrofuran **5.36**: To a flame dried 13x100 mm threaded culture tube was added vinyl oxirane **5.35** (10 mg, 0.046 mmol) in dry toluene (0.35 mL). The culture tube was fitted with a threaded septum cap and then submerged in an oil bath at 150ºC. A syringe pump was used to add toluene over 10 hours (0.1 mL, 0.1 mol%/hour) which contained $Cu(hfacac)_2$ (1.1 mg, 0.0022 mmol, 0.05 equiv.). The solution was heated for a total of 13 hours and then cooled to room temperature. The reaction mixture was filtered through neutral alumina (activity grade 1) washing with ethyl acetate and then purified by flash chromatography on silica gel (10% ether : 90% pentane, anisaldehyde) to yield 2,5-dihydrofuran **5.36** (7.0 mg, 70%, 0.032 mmol), (Crude diastereomeric ratio 10:1, purified >20:1 *cis:trans*).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.24 (m, 5H), 5.81 – 5.78 (m, 1H), 5.77 – 5.73 (m, 1H), 4.95 – 4.84 (m, 2H), 4.53 (d, *J* = 11.8, 1H), 4.49 (d, *J* = 11.8, 1H), 3.62 (dd, *J* = 6.9, 6.0, 2H), 1.93 (dtd, *J* = 12.0, 7.1, 4.9, 1H), 1.88 – 1.79 (m, 1H), 1.26 (d, *J* = 6.3, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.7, 131.6, 130.0, 128.6, 127.9, 127.7, 83.7, 81.9, 73.3, 67.4, 37.6, 23.2. **HRMS** (EI^+) *m/z* 218.13063 [calculated mass for $C_{14}H_{18}O_2$ (M^+) 218.13068].



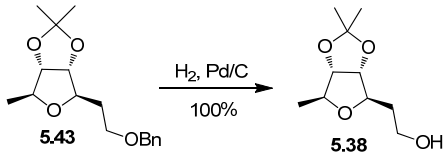
Diol **5.37**: To a scintillation vial containing acetone (0.2 mL), water (0.2 mL), dihydrofuran **5.36** (0.005 g, 0.023 mmol), and 4-methylmorpholine *N*-oxide (8.1 mg, 0.069 mmol, 3 equiv.) was added OsO_4 (2.5% in *t*BuOH, 0.1 mL, 0.3 equiv.). After 12 hours, the reaction was quenched with a solution of sodium bisulfite and diluted with ethyl acetate. The reaction was stirred vigorously for several hours and then the layers were separated. The aqueous layer was extracted with ethyl acetate three additional times. The combined organic portions were dried over Na_2SO_4. The solvent was removed *in vacuo* and purified by chromatography (80% ether: 20% pentane, anisaldehyde) to yield diol **5.37** (4.0 mg, 0.016 mmol, 69% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 – 7.28 (m, 5H), 4.54 (d, *J* = 1.1, 2H), 3.92 – 3.84 (m, 2H), 3.78 – 3.62 (m, 4H), 2.90 (bd, *J* = 6.0, 1H), 2.76 (bs, 1H), 2.06 – 1.86 (m, 2H), 1.27 (d, *J* = 6.5, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.4, 128.9, 128.3, 128.1, 82.1, 80.7, 76.7, 75.6, 73.8, 68.2, 34.1, 19.8. **IR** (neat) 3374, 2905, 2865, 1453, 1363, 1311, 1205, 1073, 1027, 882, 735, 697 cm^{-1}. **HRMS** (ESI) *m/z* 275.1251 [calculated mass for $C_{14}H_{20}O_4$ ($M+Na^+$) 275.1259].



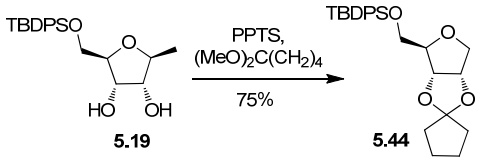
Acetonide **5.43**: To a scintillation vial was added diol **5.37** (4 mg, 0.016 mmol, 1 equiv.) and CH_2Cl_2 (0.3 mL). Then pyridinium *p*-toluenesulfonate (0.8 mg, 0.0032 mmol, 0.2 equiv.) and 2,2-dimethoxypropane (16.5 mg, 0.158 mmol, 10 equiv.) were added to the vial. The reaction was stirred for 12 hours. It was diluted with methylene chloride and washed with $NaHCO_3$ and brine. The solution was dried over Na_2SO_4 and purified by chromatography (30% ether : 70% pentane, anisaldehyde) to give the expected acetonide (2.0 mg, 0.0068 mmol, 43% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.27 (m, 5H), 4.56 – 4.47 (m, 2H), 4.43 (dd, *J* = 7.0, 4.9, 1H), 4.23 (dd, *J* = 7.0, 5.2, 1H), 3.96 – 3.86 (m, 2H), 3.67 – 3.56 (m, 2H), 1.94 (qd, *J* = 13.8, 7.1, 2H), 1.53 (s, 3H), 1.33 (s, 3H), 1.29 (d, *J* = 6.4, 3H). **^{13}C NMR** (126 MHz, $CDCl_3$) δ 138.7, 128.5, 127.8, 127.7, 115.0, 86.4, 85.6, 81.7, 80.2, 73.2, 67.2, 34.2, 27.6, 25.7, 19.2. **HRMS** (EI^+) *m/z* 292.16637 [calculated mass for $C_{17}H_{24}O_4$ (M^+) 292.16746].



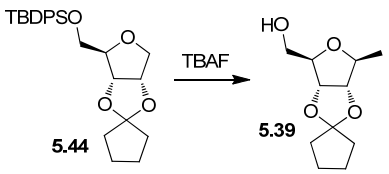
Primary Alcohol **5.38**: To a small vial with a septum cap was added acetonide (0.8 mg, 0.0027 mmol). Then Pd/C (0.8 mg, 10%) was added along with methanol (0.5 mL). A balloon of hydrogen was attached to the vial and it was stirred at room temperature for 15 hours. The solution was filtered through celite and the solvent removed *in vacuo* to yield the primary alcohol **5.38** in quantitative yield (0.5 mg).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.44 – 4.37 (m, 1H), 4.28 (dd, *J* = 7.1, 4.9, 1H), 3.99 – 3.90 (m, 2H), 3.84 – 3.78 (m, 2H), 2.33 – 2.27 (m, 1H), 1.99 – 1.90 (m, 1H), 1.90 – 1.79 (m, 1H), 1.54 (s, 3H), 1.34 (s, 3H), 1.32 (d, *J* = 6.4, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 115.4, 86.2, 85.3, 84.0, 80.6, 61.2, 35.8, 27.6, 25.7, 19.3.



Cyclopropylidene **5.44**: To a 25 mL flask equipped with a stir bar was added methylene chloride (9 mL), diol **5.19** (0.340 g, 0.88 mmol), pyridinium p-toluenesulfonate (0.040 g, 0.16 mmol, 0.2 equiv.), and dimethoxylcyclopentane (1.1 g, 8.5 mmol, 10 equiv.). The reaction was stirred for 12 hours at room temperature. It was diluted with methylene chloride and washed with $NaHCO_3$ and brine. The solution was dried over Na_2SO_4 and purified by chromatography (20% ether : 80% pentane) to give cyclopentylacetal (0.297 g, 0.66 mmol, 75% yield).

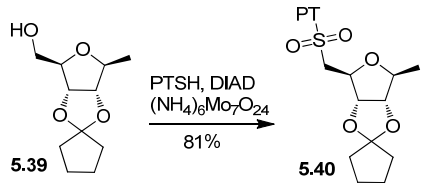
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 – 7.65 (m, 4H), 7.44 – 7.33 (m, 6H), 4.67 (dd, *J* = 6.8, 3.7, 1H), 4.21 (dd, *J* = 6.7, 5.1, 1H), 4.06 – 3.96 (m, 2H), 3.79 (d, *J* = 3.9, 2H), 1.96 (t, *J* = 7.6, 2H), 1.78 – 1.61 (m, 6H), 1.31 (d, *J* = 6.3, 1H), 1.07 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 135.8(3), 135.7(6), 133.5, 133.3, 129.9, 129.8, 127.8(4), 127.7(9), 123.6, 86.1, 84.0, 82.4, 80.2, 64.4, 37.0, 36.9, 27.0, 23.7, 23.3, 19.4, 19.3. **IR** (neat) 2960, 2858, 1589, 1428, 1336, 1112, 979, 823, 702 cm^{-1}.



Primary alcohol **5.39:** To a 25 mL flask equipped with a stir bar was added cyclopentylacetal (0.297 g, 0.66 mmol) and tetrahydrofuran (6.5 mL). The solution

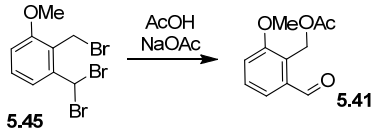
was cooled to 0°C and tetrabutylammonium fluoride (0.79 mL, 1 M in THF, 0.79 mmol, 1.2 equiv.) was added dropwise. The reaction was stirred for 1 hour at 0°C and then 1 hour at room temperature. The reaction was quenched with water and extracted with CH_2Cl_2. The solution was dried over Na_2SO_4 and purified by chromatography (50% ether : 50% pentane) to give **5.39** (0.140 g, 0.65 mmol, 99% yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.53 (dd, *J* = 7.1, 4.5, 1H), 4.18 (dd, *J* = 7.1, 5.2, 1H), 4.04 – 3.94 (m, 2H), 3.79 (dd, *J* = 11.9, 3.4, 1H), 3.66 (dd, *J* = 12.0, 4.7, 1H), 2.80 (bs, 1H), 1.96 (dd, *J* = 11.1, 4.3, 2H), 1.76 – 1.62 (m, 6H), 1.31 (d, *J* = 6.4, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 124.2, 86.0, 84.0, 81.6, 80.1, 62.7, 36.7(7), 36.7(5), 23.6, 23.2, 18.9. **HRMS** (EI^+) *m/z* 214.12064 [calculated mass for $C_{11}H_{18}O_4$ (M^+) 214.12051].



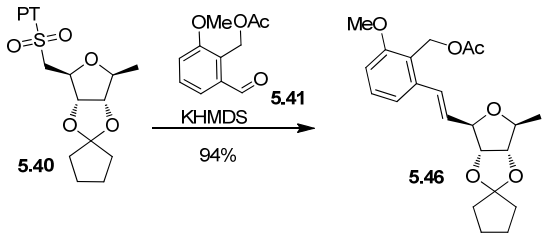
Sulfone **5.40**: To a 4 mL reaction vial containing dry methylene chloride (0.42 mL) and 1-phenyl-1H-tetrazole-5-thiol (0.045 g, 0.252 mmol) was added triphenylphosphine (0.066 g, 0.252 mmol) at 0°C. Primary alcohol **5.39** (0.036 g, 0.168 mmol) was then dissolved in dry methylene chloride (0.23 mL) and added drop-wise to the above solution over 2 minutes. After complete addition, diisopropyl azodicarboxylate (DIAD) (0.05 mL, 0.252 mmol) was added slowly over 30 minutes by syringe and the reaction was allowed to stir an additional 90 minutes to consume all starting alcohol. The reaction was then concentrated to an oil and subsequently dissolved in ethanol (1.08 mL). To a 4 mL reaction vial containing ammonium molybdate (0.041 g, 0.033 mmol) was added 30% hydrogen peroxide solution (0.15 mL, 1.68 mmol) at 0°C which immediately turns yellow in color. The crude reaction mixture in ethanol was then added to the molybdate solution, the bath was removed and the reaction was allowed to stir 14 hours at room temperature. The reaction was then quenched by adding saturated sodium sulfite solution (2 mL), extracted with dichloromethane and dried over anhydrous $NaSO_4$. The organics were concentrated and purified by flash chromatography (30% ethyl acetate : 70% hexanes, anisaldehyde) to give sulfone **5.40** (0.055 g, 81%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 – 7.55 (m, 5H), 4.47 (dd, *J* = 6.8, 5.4, 1H), 4.27 (dd, *J* = 12.3, 5.4, 1H), 4.19 (dd, *J* = 6.8, 4.4, 1H), 3.94 – 3.88 (m, 3H), 1.95 – 1.87 (m, 2H), 1.73 – 1.60 (m, 6H), 1.13 (d, *J* = 6.4, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 153.8, 133.0, 131.4, 129.5, 125.6, 125.0, 85.4, 83.6, 80.6, 77.5, 58.9, 36.6, 36.6, 23.5, 23.0, 18.7. **IR** (neat) 2973, 2941, 1498, 1353, 1154, 1106, 1054, 915, 764 cm^{-1}. **HRMS** (ESI) *m/z* 407.1389 [calculated mass for $C_{18}H_{23}N_4O_5S$ ($M+H^+$) 407.1389].



Aldehyde **5.41**: To a 50 mL flask was added the tribromide product derived from dimethyl anisole[5] (1.0 g, 2.68 mmol) and glacial acetic acid (16.0 mL) with a reflux condenser attached. To this was added sodium acetate (4.01 g, 29.49 mmol) and water (4.29 mL) and the reaction was refluxed at 110°C for 7 hours. After cooling to room temperature, the reaction was diluted with diethyl ether and washed with water, saturated bicarbonate, and sodium carbonate. The organics were dried over $NaSO_4$, concentrated, and purified using flash chromatography (30% ethyl acetate : 70% hexanes, anisaldehyde) to give **5.41** (0.498g, 90%).

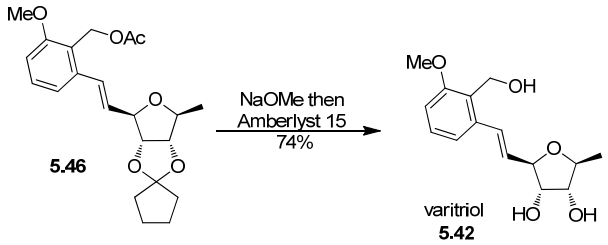
^{1}H NMR (400 MHz, $CDCl_3$) δ 10.29 (s, 1H), 7.56 – 7.45 (m, 2H), 7.21 – 7.15 (m, 1H), 5.56 (s, 2H), 3.90 (s, 3H), 2.06 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 191.9, 170.9, 158.6, 136.1, 130.4, 125.1, 122.9, 116.4, 56.3, 56.0, 21.0. **IR** (neat) 2975, 2942, 2843, 1736, 1697, 1587, 1472, 1381, 1270, 1241, 1026. **HRMS** (EI^+) *m/z* 208.07384 [calculated mass for $C_{11}H_{12}O_4$ ($M^{+)}$ 208.07356].



Protected Varitriol. A fresh stock solution of potassium bis-(trimethylsilyl) amide (KHMDS) was prepared by mixing hexa-methyldisilazane (0.051 mL, 0.24 mmol), dry tetrahydrofuran (5 mL), and 30% potassium hydride suspension (0.032g, 0.24 mmol) at room temperature. To a 4 mL reaction vial was added sulfone **5.40** (0.020 g, 0.050 mmol) dissolved in a 4:1 mixture of dimethylformamide (DMF) and hexamethylphosphoramide (HMPA) (0.2 mL) at -78°C. The freshly prepared KHMDS (1.0 mL, 0.048 mmol) was added and the reaction was allowed to stir 10 minutes. Aldehyde **5.41** (0.012 g, 0.055 mmol) was dissolved in the DMF:HMPA solvent mixture (0.2 mL) and subsequently added to the reaction. The reaction was allowed to slowly warm to room temperature and then stirred 12 hours. The reaction was quenched by adding water (1 mL), extracted with diethyl ether, dried over $NaSO_4$, and purified by flash chromatography (30% ethyl acetate : 70% hexanes, anisaldehyde) to give protected varitriol (0.018 g, 94%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.30 (t, *J* = 8.0, 1H), 7.13 (d, *J* = 8.0, 1H), 6.95 (d, *J* = 15.7, 1H), 6.84 (d, *J* = 8.0, 1H), 6.16 (dd, *J* = 15.7, 6.4, 1H), 5.27 (s, 2H), 4.51 – 4.41 (m, 2H), 4.28 (dd, *J* = 6.5, 4.6, 1H), 4.10 – 4.02 (m, 1H), 3.83 (s, 3H), 2.06 (s, 3H), 2.05 – 1.97 (m, 2H), 1.78 – 1.63 (m, 6H), 1.36 (d, *J* = 6.4, 3H). **^{13}C NMR** (126 MHz,

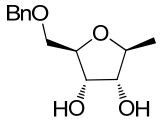
$CDCl_3$) δ 171.4, 158.6, 138.9, 131.0, 130.1, 129.6, 124.6, 121.5, 119.0, 110.3, 86.5, 85.8, 84.6, 80.2, 57.9, 56.1, 37.1, 37.0, 23.8, 23.4, 21.3, 19.4. **IR** (neat) 2970, 2943, 1735, 1580, 1473, 1379, 1242, 1102, 1054 cm^{-1}. **HRMS** (ESI) *m/z* 411.1770 [calculated mass for $C_{22}H_{28}O_6Na$ ($M+Na^+$) 411.1784].



Varitriol. To a 4 mL reaction vial was added protected varitriol (0.015 g, 0.039 mmol) and methanol (0.8 mL) at room temperature. To this was added solid sodium methoxide (0.010 g, 0.195 mmol) and the reaction was stirred for 1 hour until starting material was consumed. At this time the reaction was filtered through a plug of silica gel with ethyl acetate to give crude primary alcohol. The crude primary alcohol was dissolved in methanol (0.6 mL) and Amberlyst 15 (5 mg) was added and the reaction was allowed to stir 1 hour until starting material was consumed. The reaction was concentrated and filtered through a plug of silica gel with ethyl acetate to give varitriol (0.008 g, 74%) which matched all known spectral data in $(CD_3)_2CO$.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31 – 7.20 (m, 1H), 7.14 – 7.02 (m, 2H), 6.83 (d, *J* = 8.0, 1H), 6.13 (dd, *J* = 15.7, 6.9, 1H), 4.87 – 4.72 (m, 2H), 4.34 (t, *J* = 6.1, 1H), 3.99 – 3.89 (m, 2H), 3.87 (s, 3H), 3.83 – 3.75 (m, 1H), 2.58 (d, *J* = 5.8, 1H), 2.43 (d, *J* = 5.6, 1H), 2.21 (t, *J* = 6.4, 1H), 1.37 (d, *J* = 6.3, 3H).

A5.2 ^{1}H and ^{13}C NMR Spectra for Chapter 5



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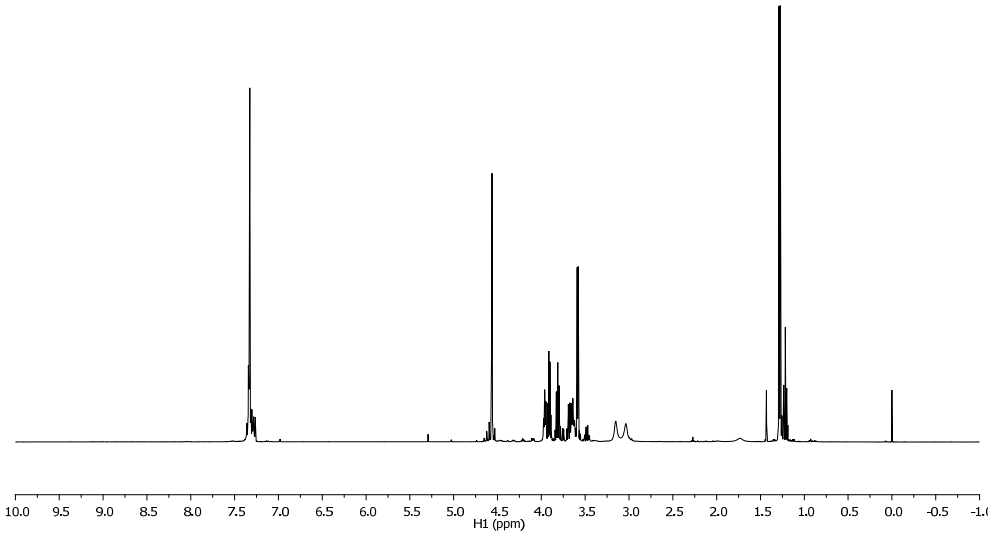

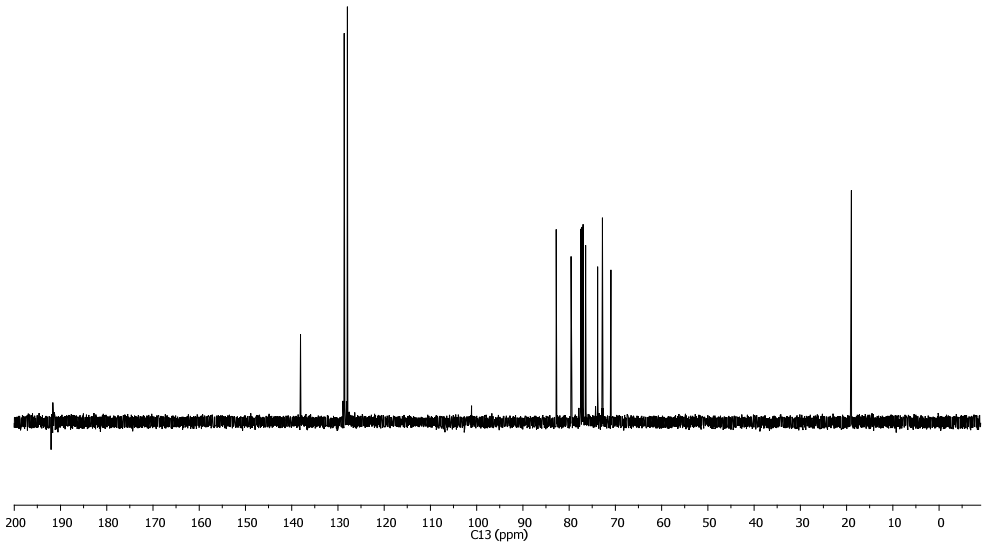

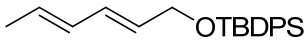
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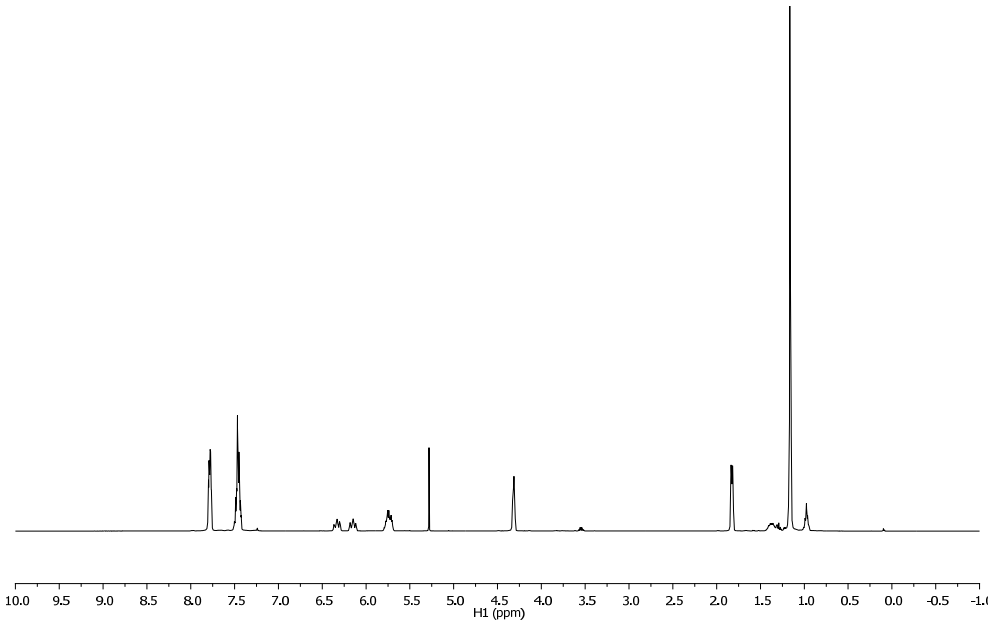
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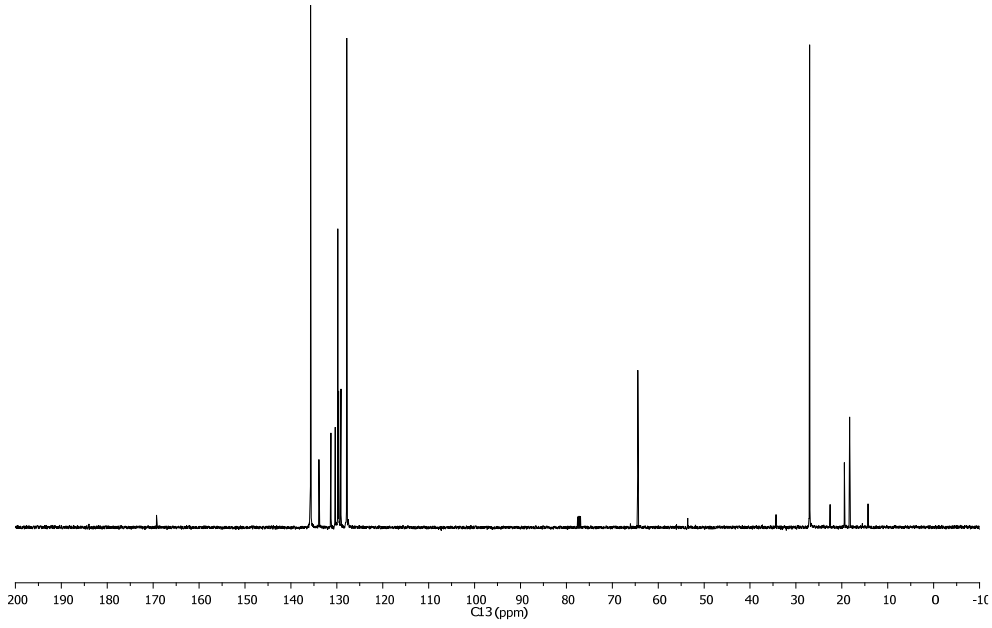
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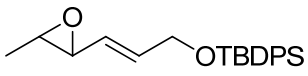
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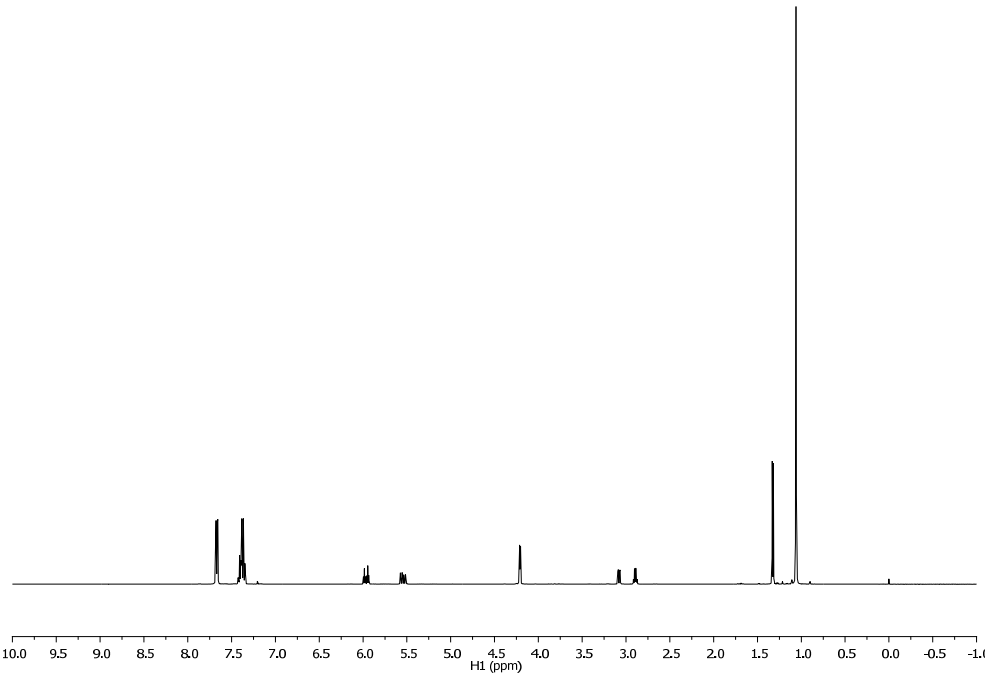
5.16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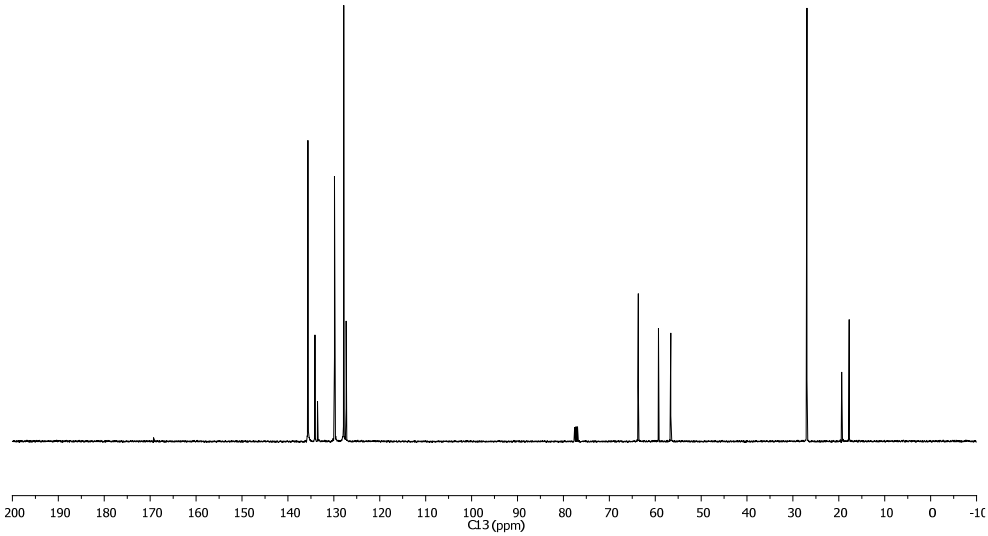
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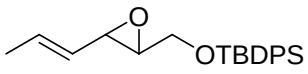
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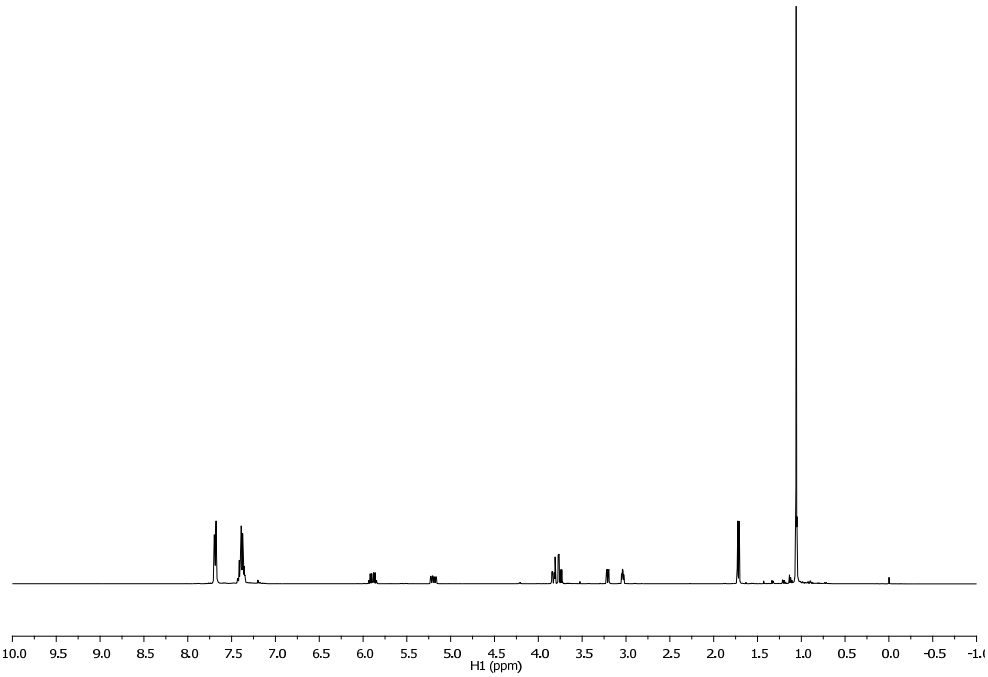
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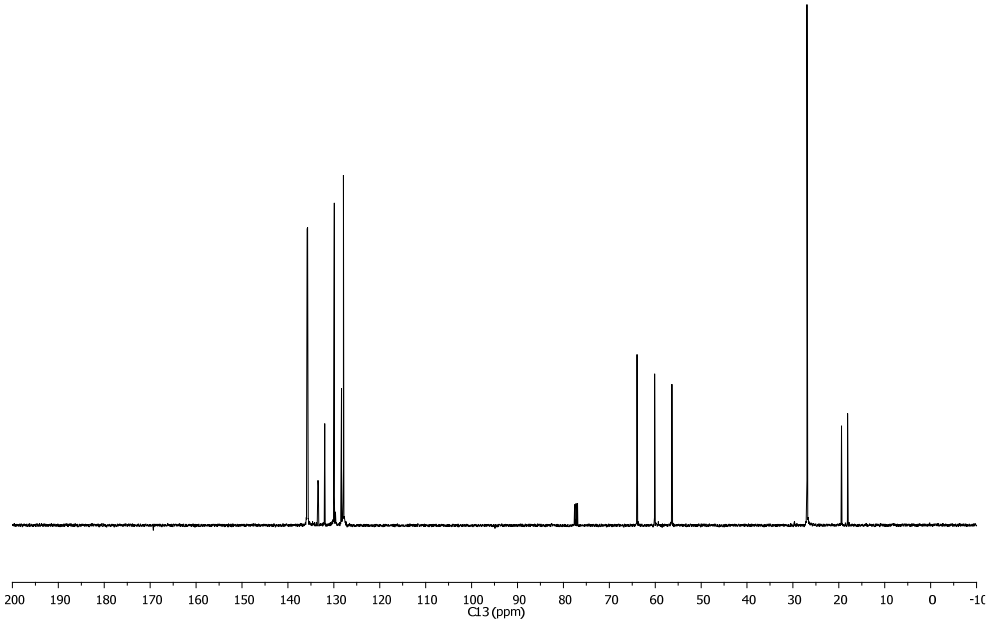
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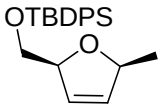
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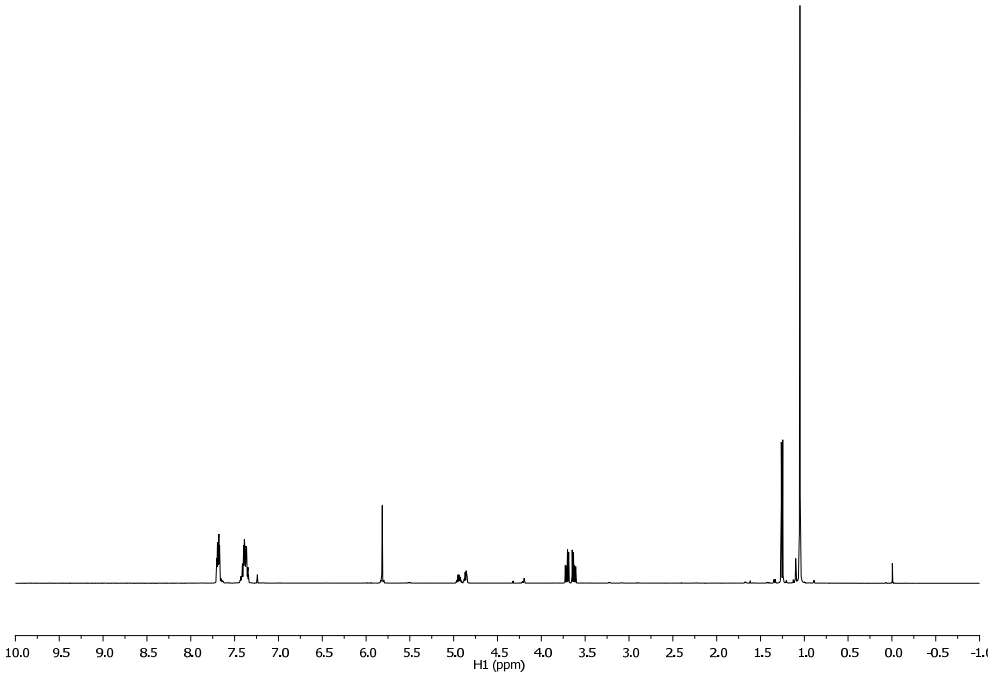
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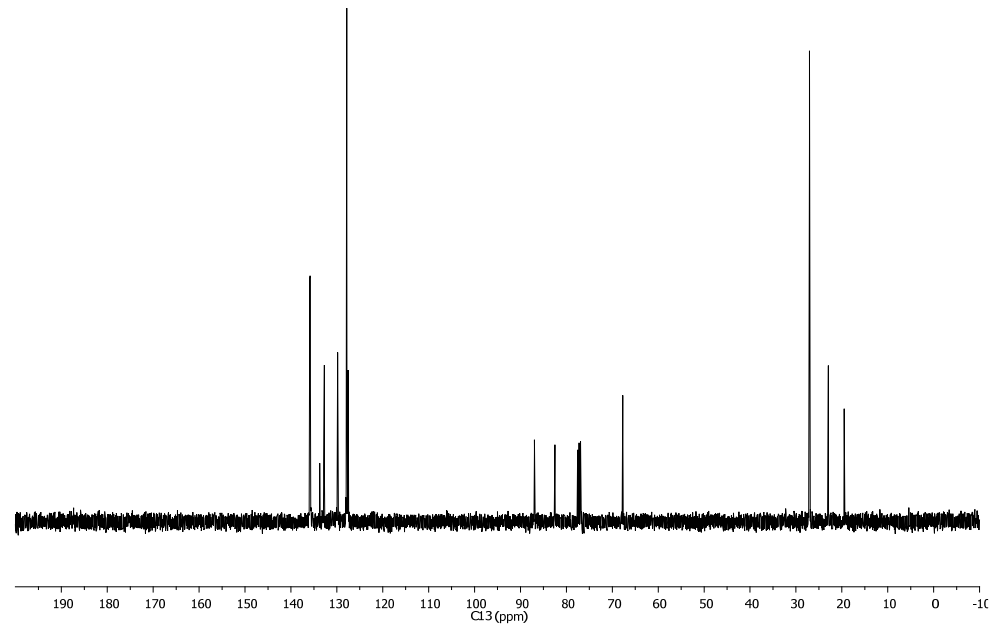
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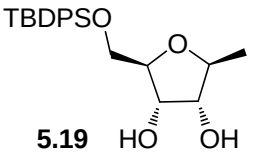
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OH

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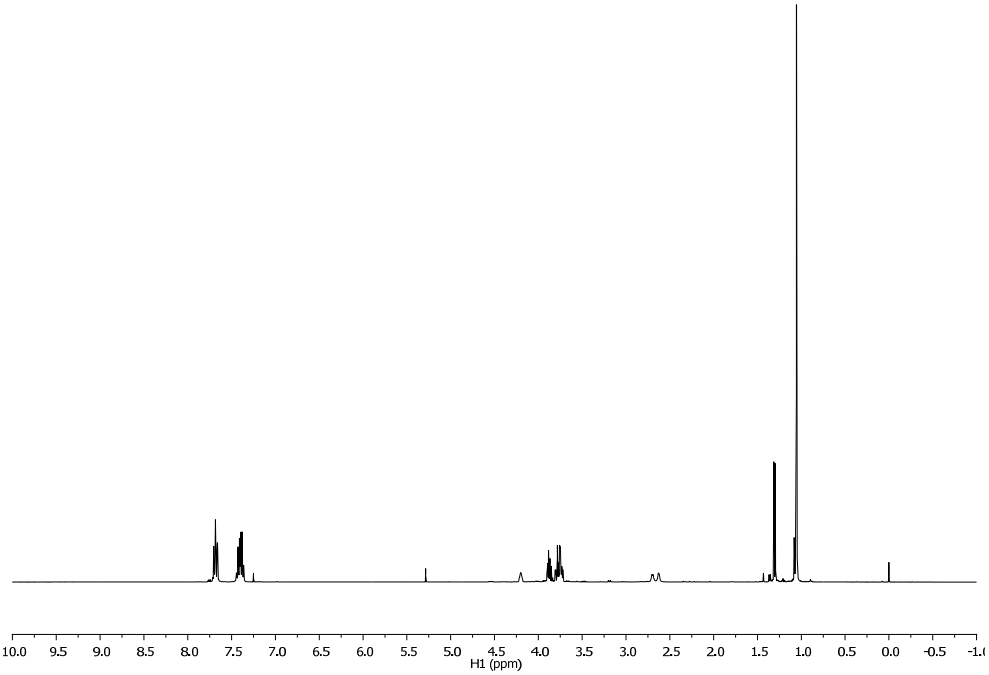
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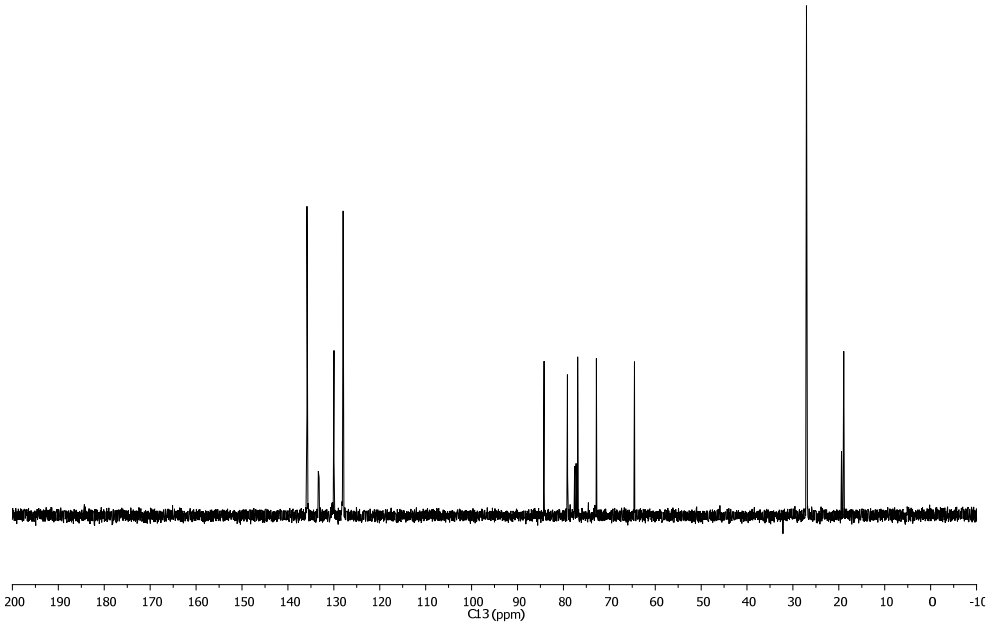
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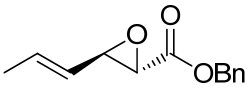
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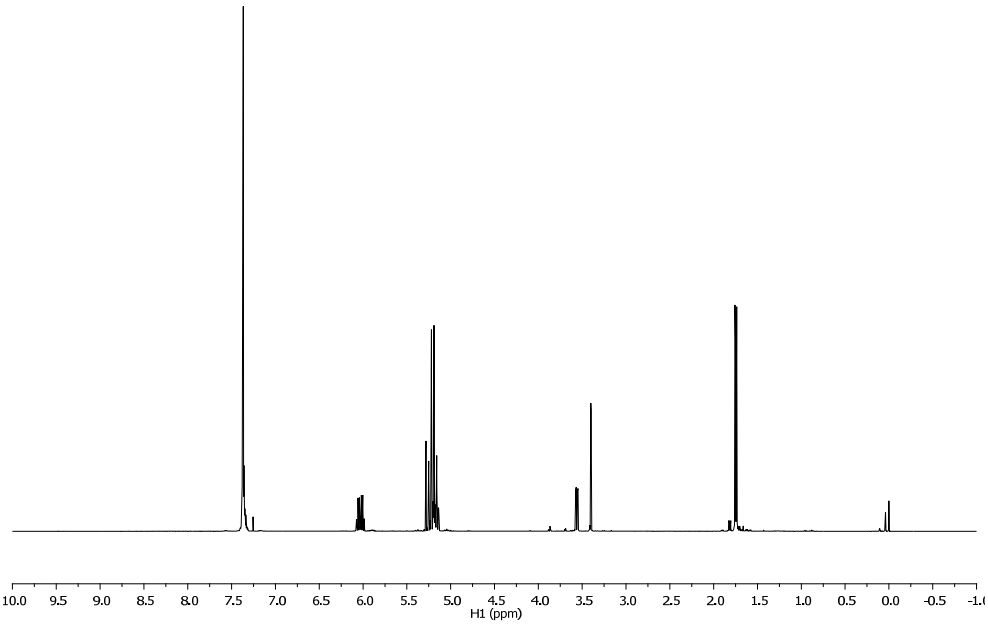
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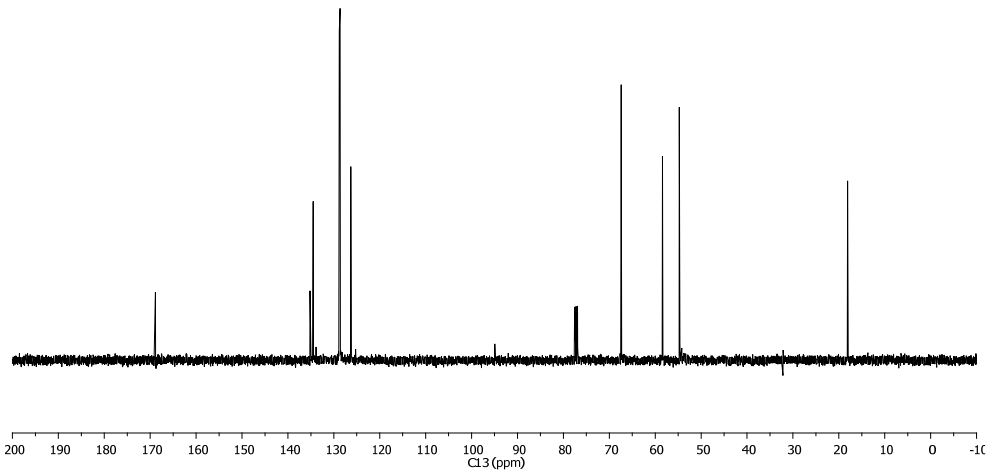
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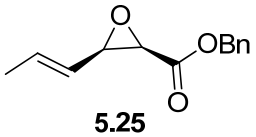
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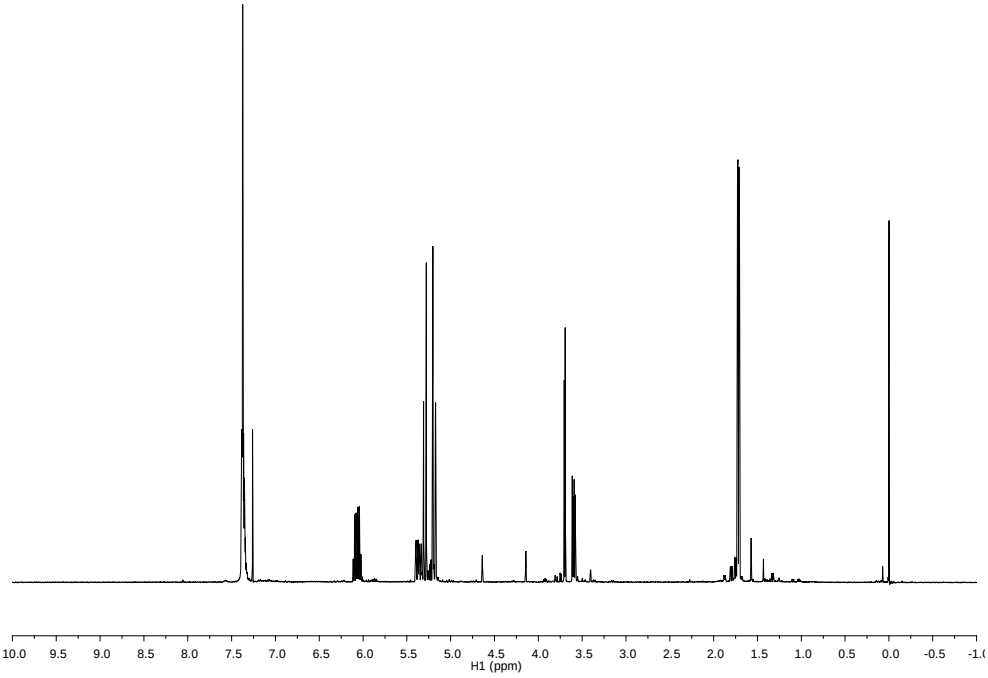
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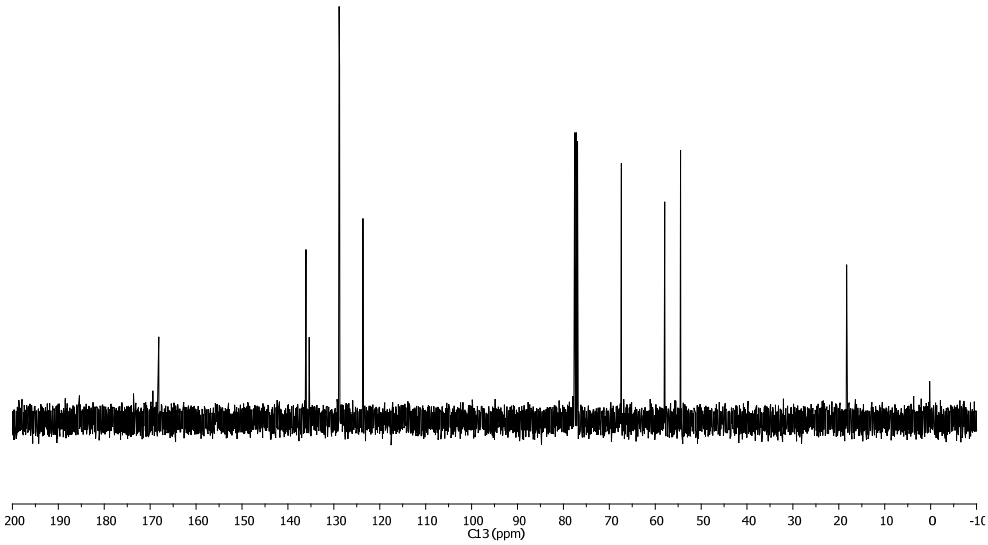
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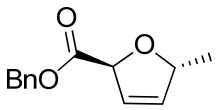
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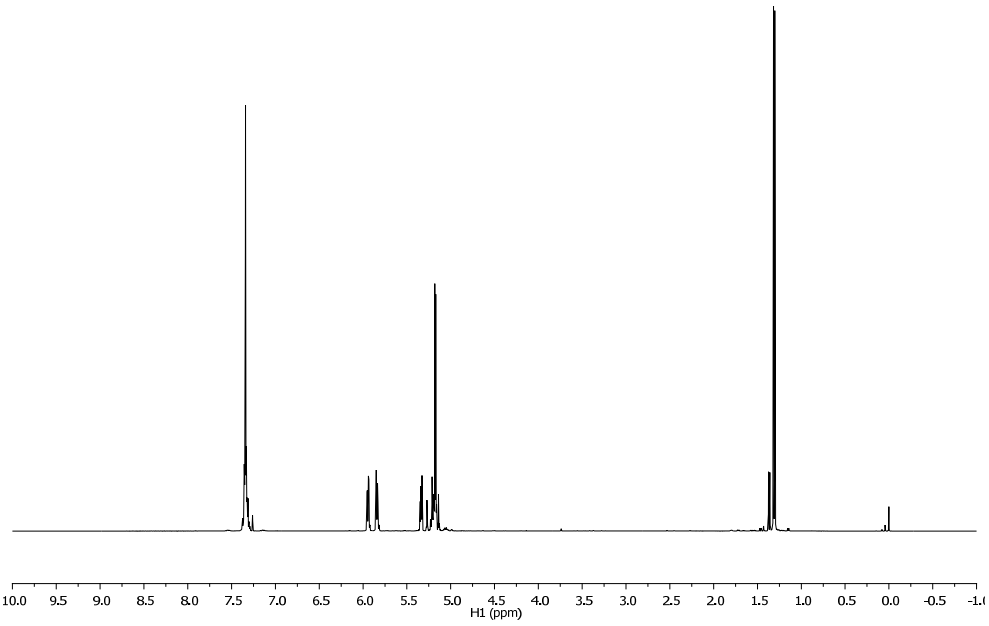
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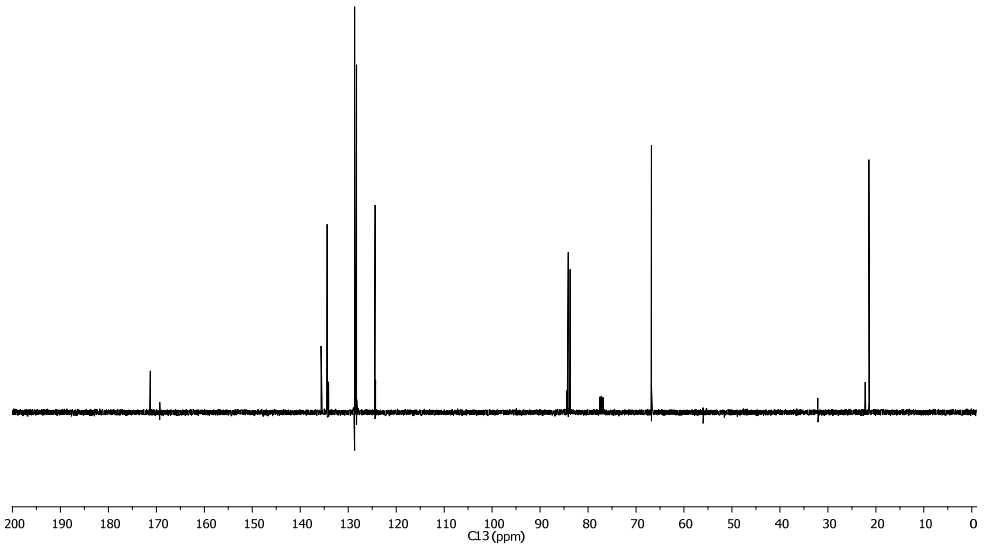
H1 (ppm)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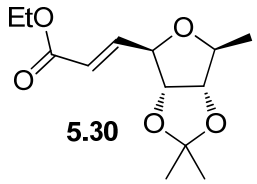
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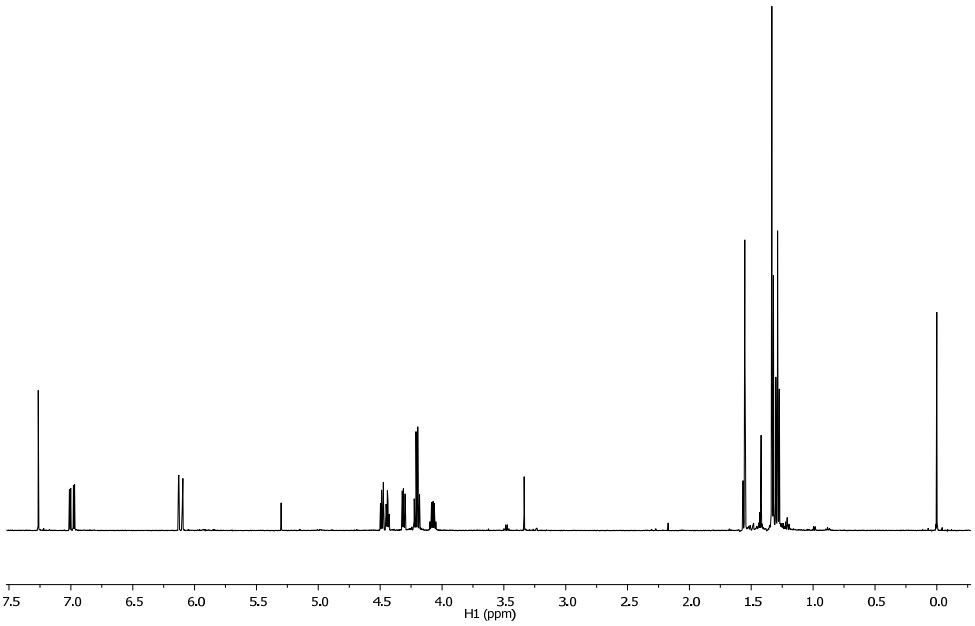
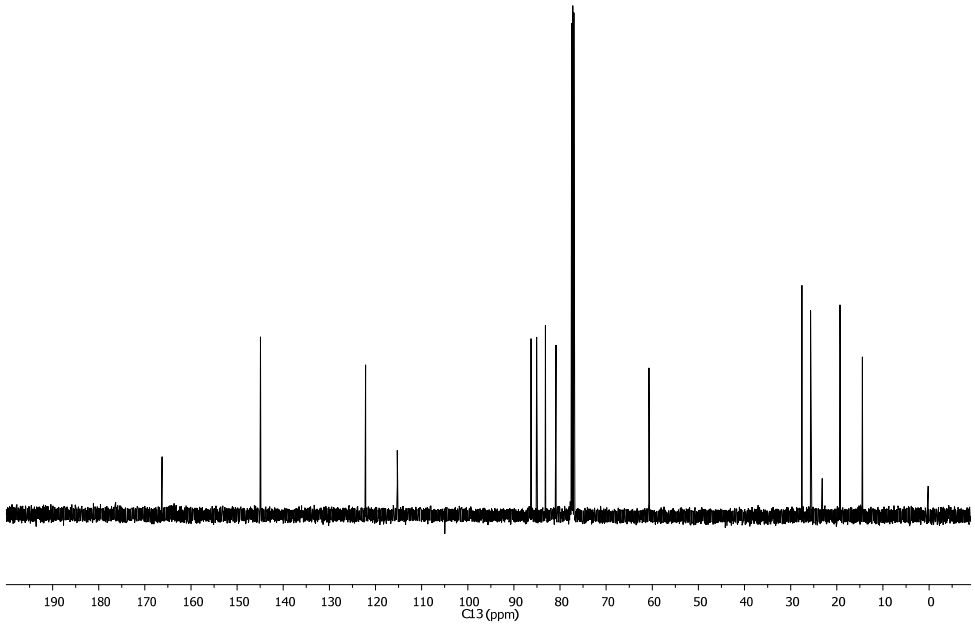
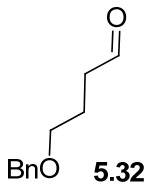
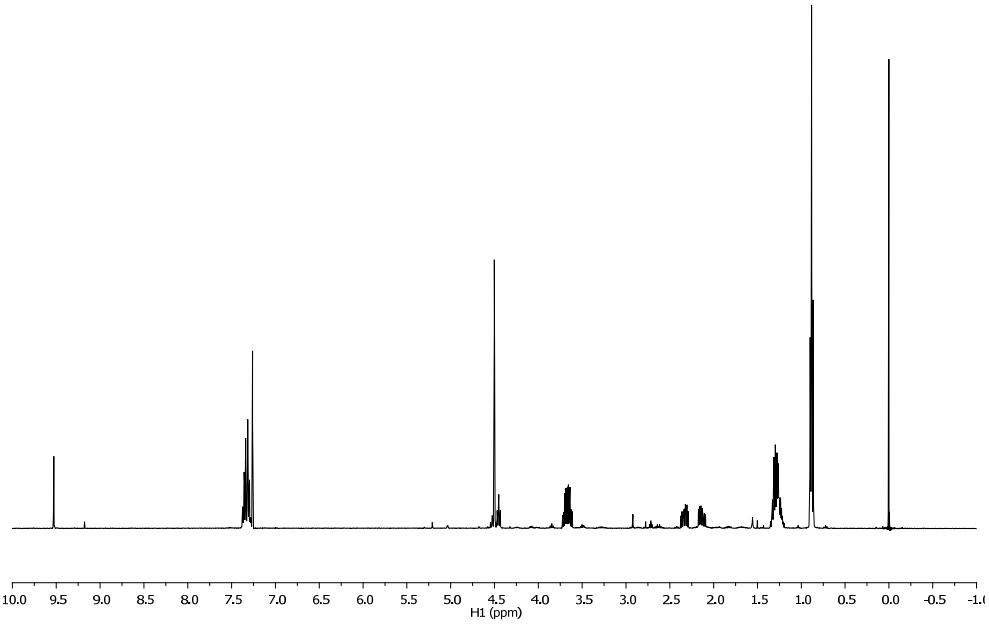

7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
H1 (ppm)


190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
C13 (ppm)


O
BnO

5.32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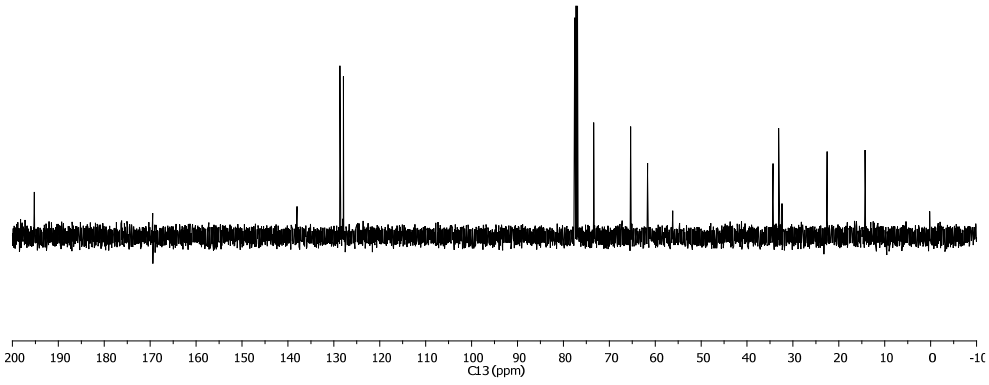
H1 (ppm)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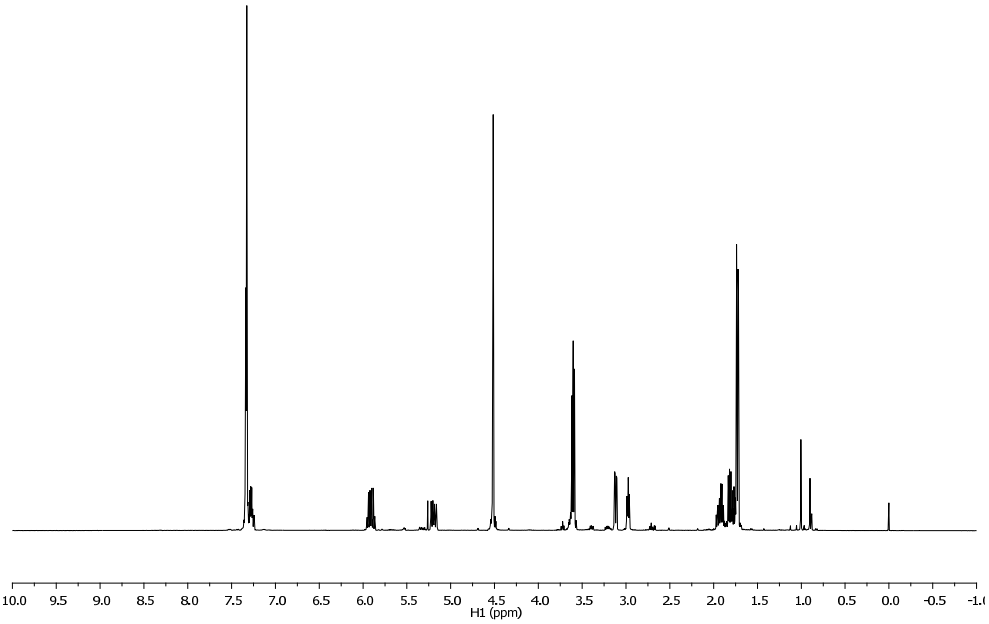
C13 (ppm)


O
OBn

5.35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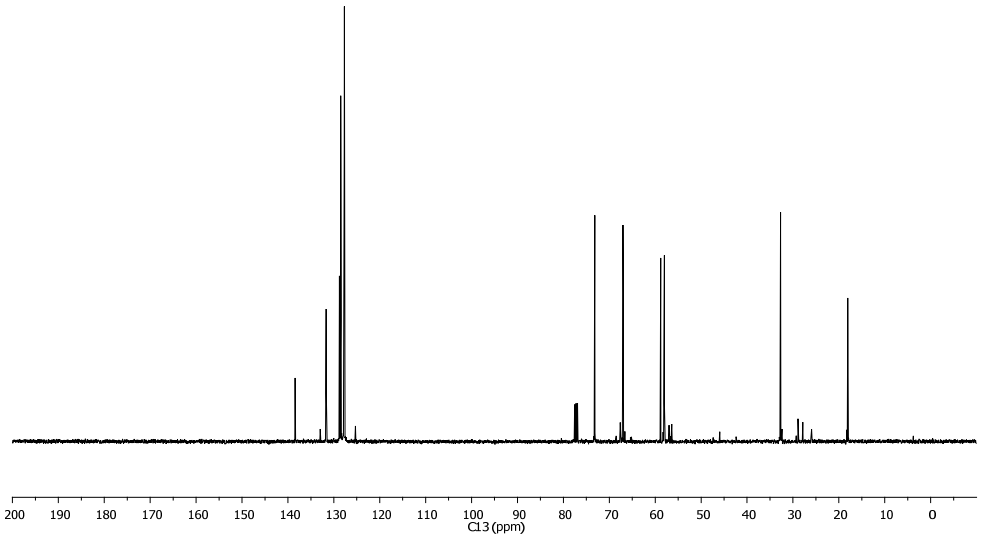
H1 (ppm)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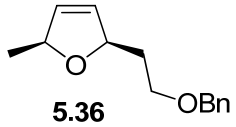
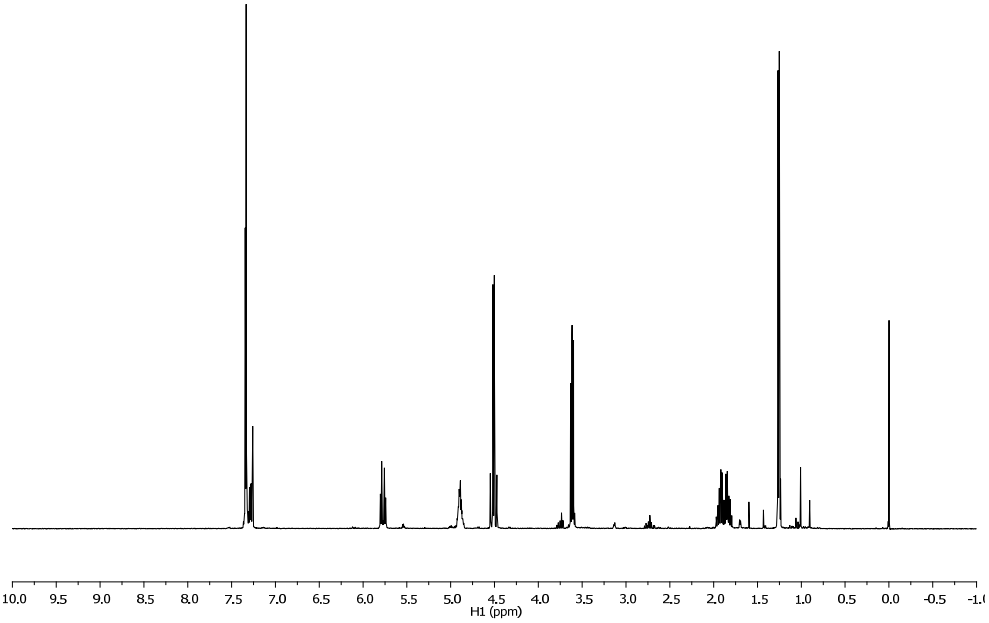
C13 (ppm)


O
OBn

5.36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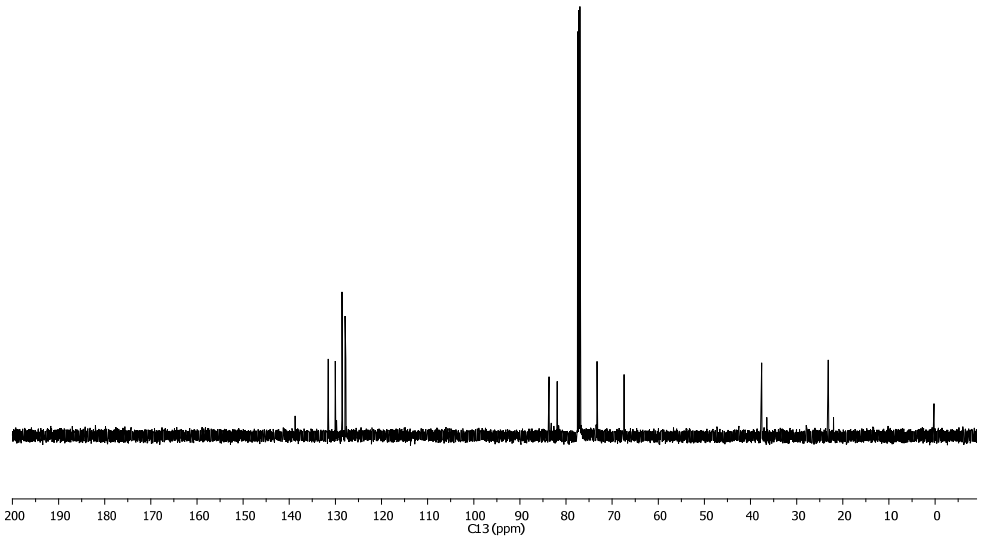
H1 (ppm)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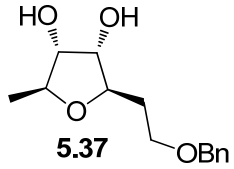
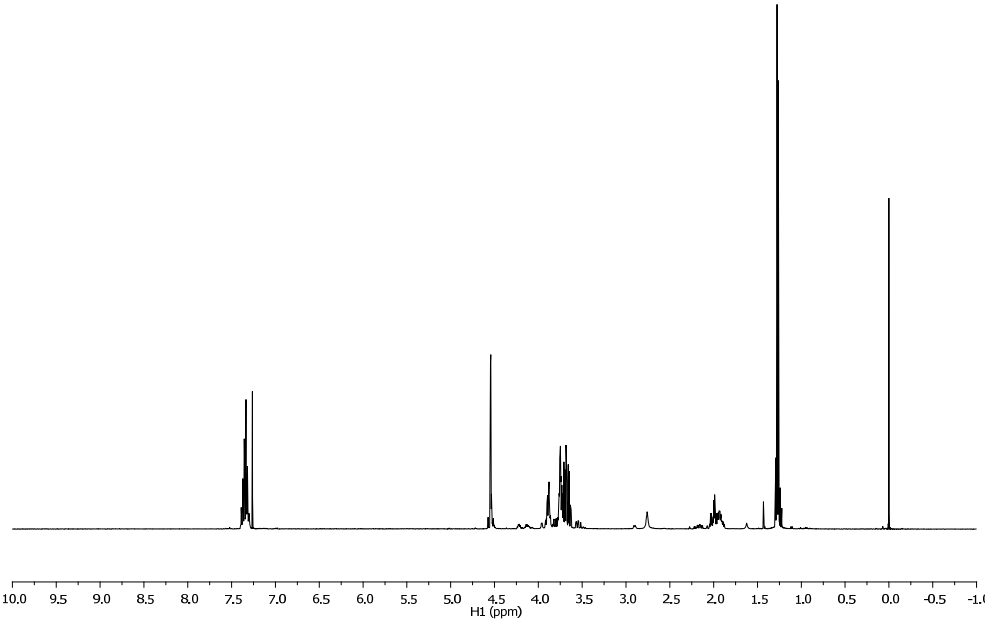
C13 (ppm)


HO
OH
O
OBn

5.37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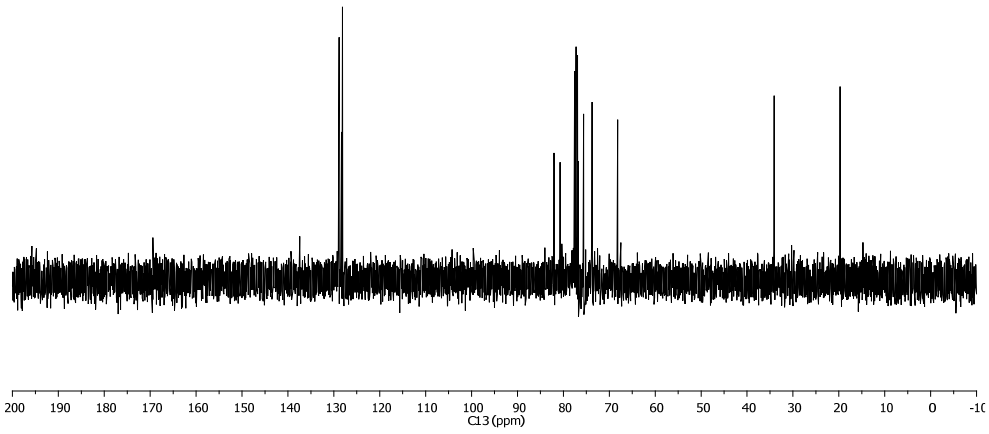
H1 (ppm)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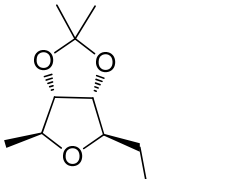
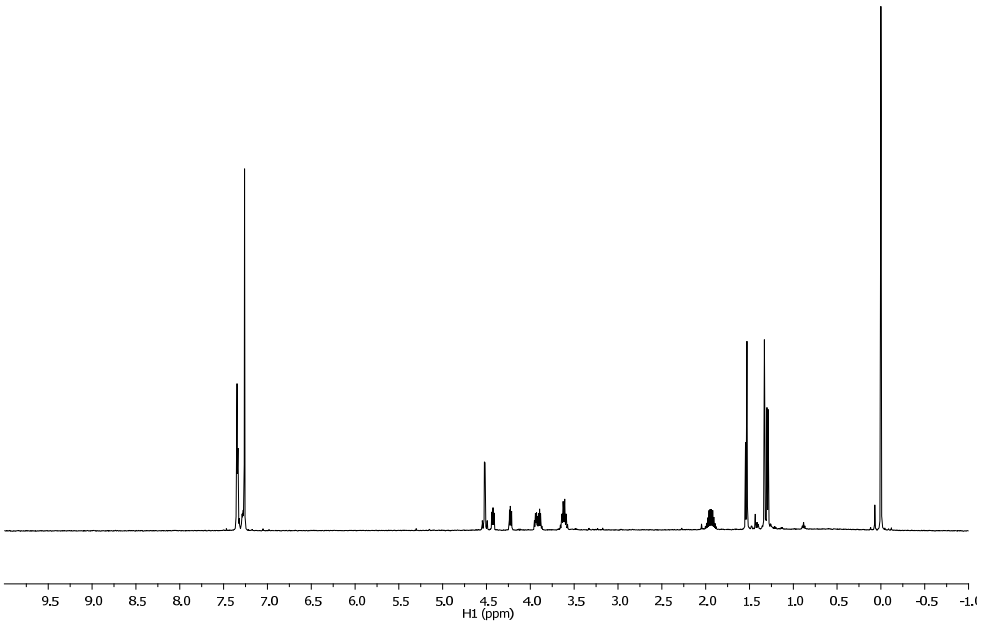
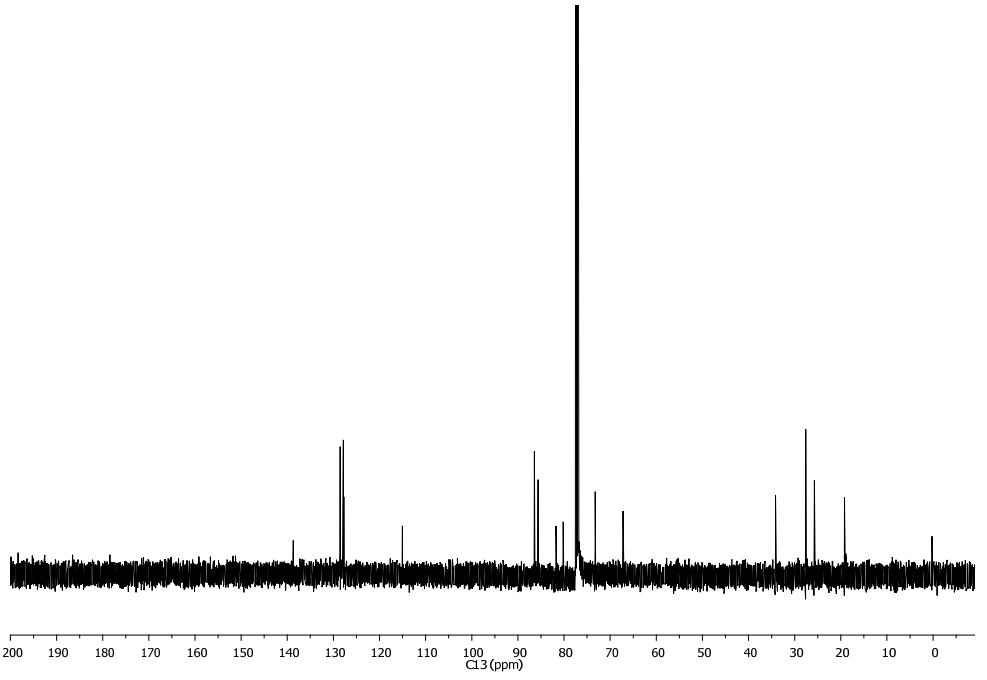
C13 (ppm)


O
O
O
OBn

5.43


9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
H1 (ppm)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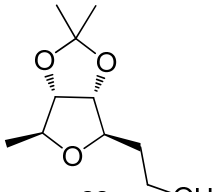
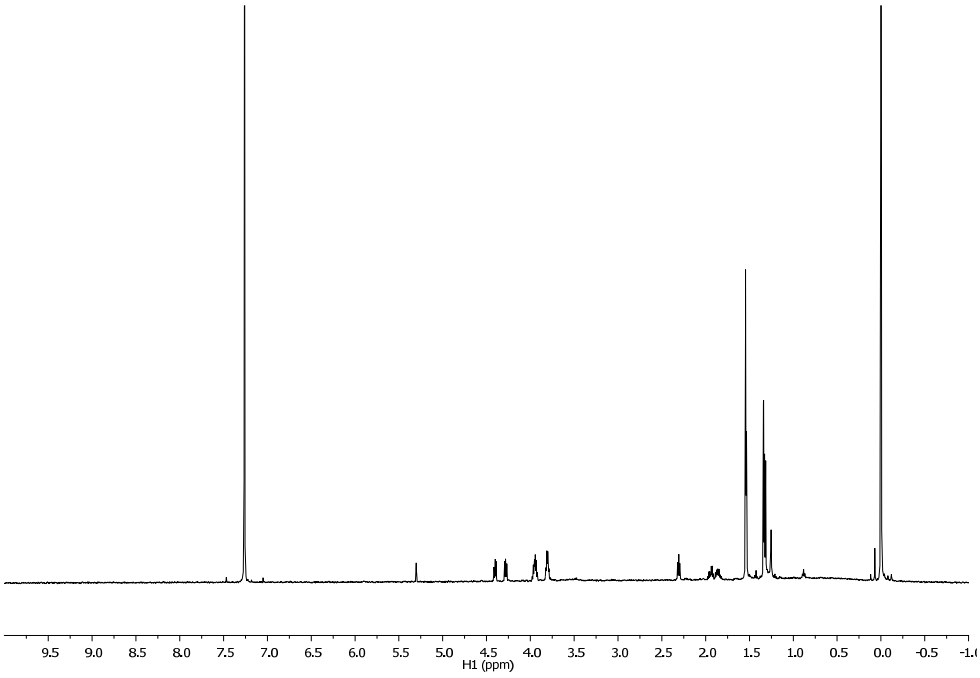
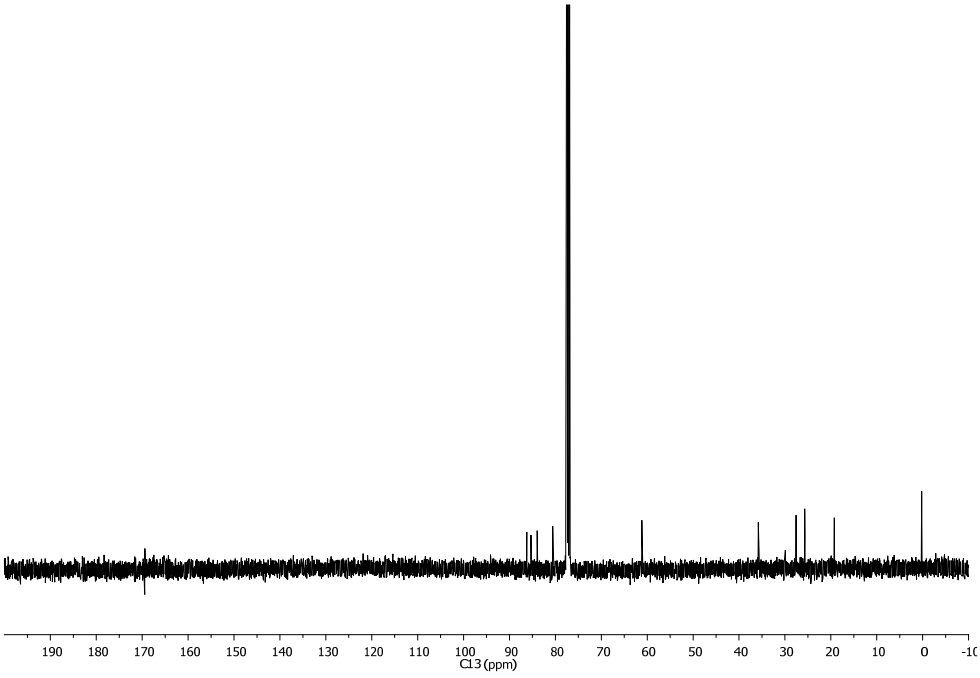
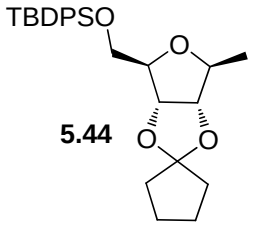
C13 (ppm)


O
O
O
OH

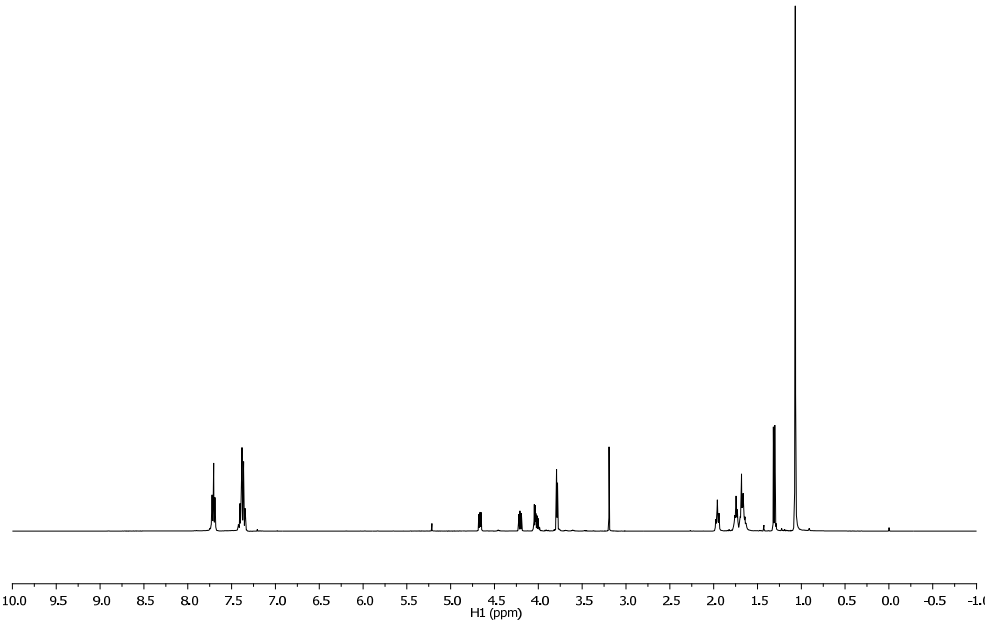
5.38

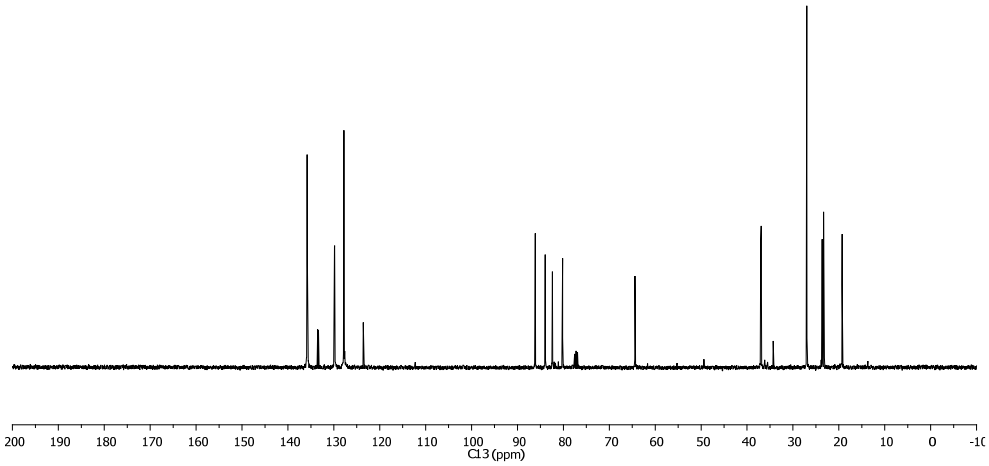

9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
H1 (ppm)


190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
C13 (ppm)


TBDPSO
O
O
O

5.44


10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
H1 (ppm)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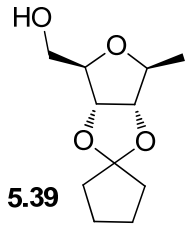
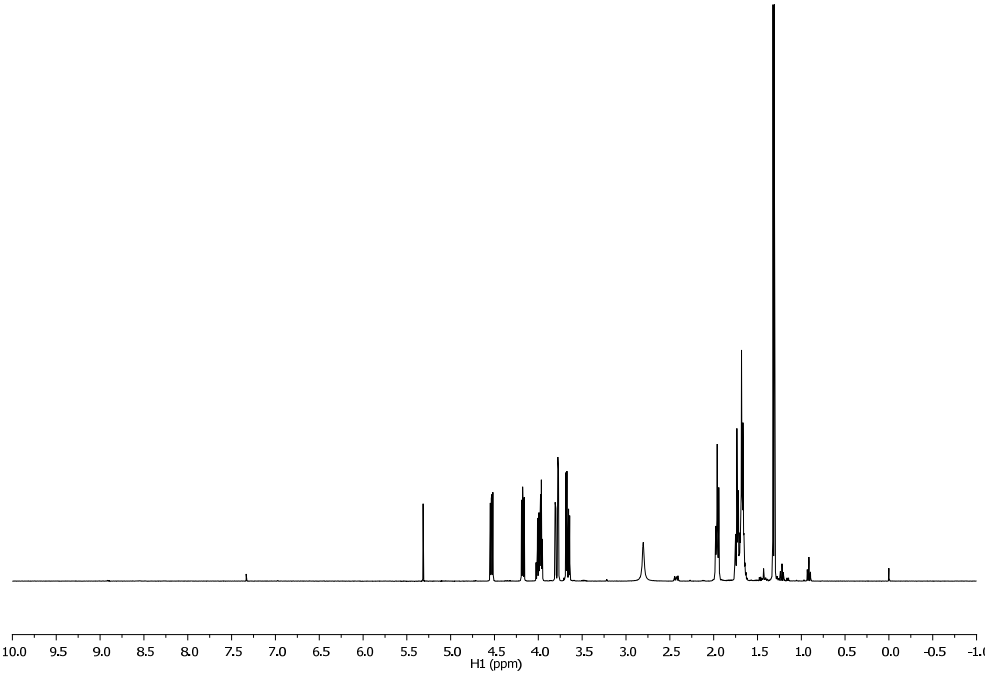
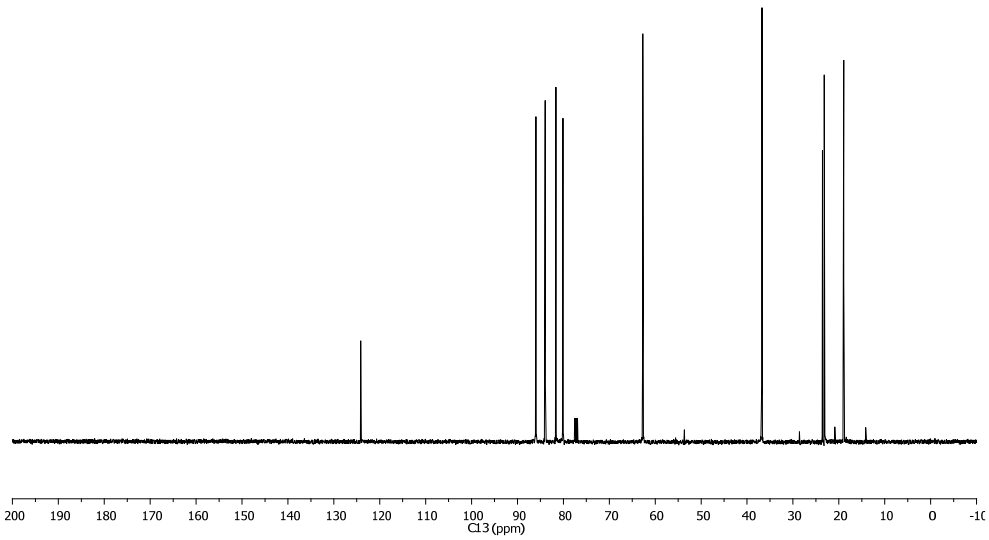
C13 (ppm)


HO
O
O
O

5.39


10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
H1 (ppm)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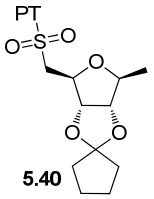
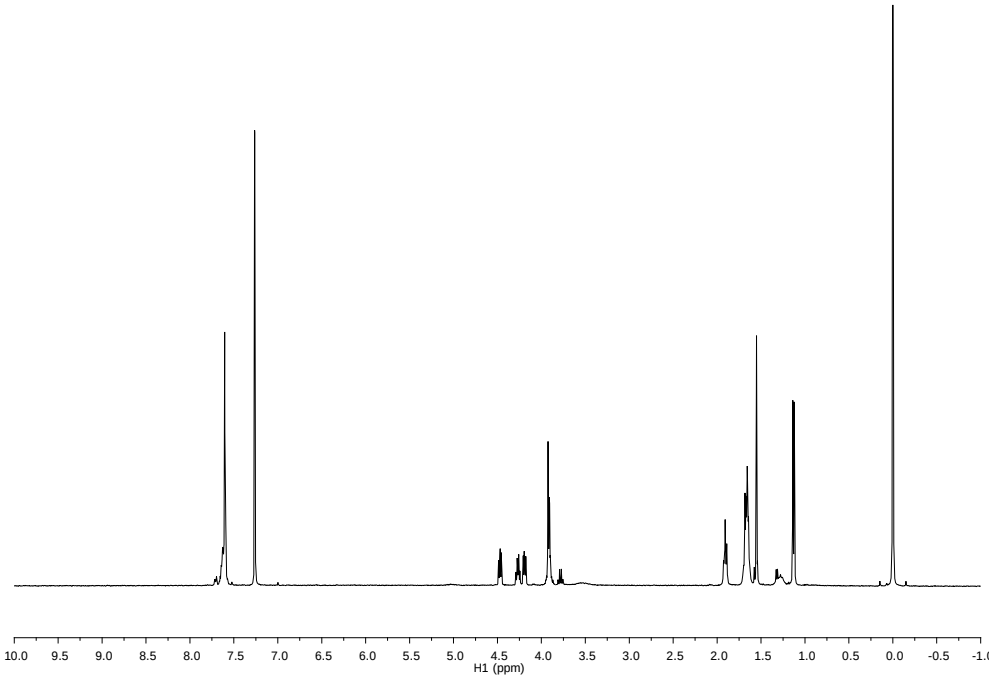
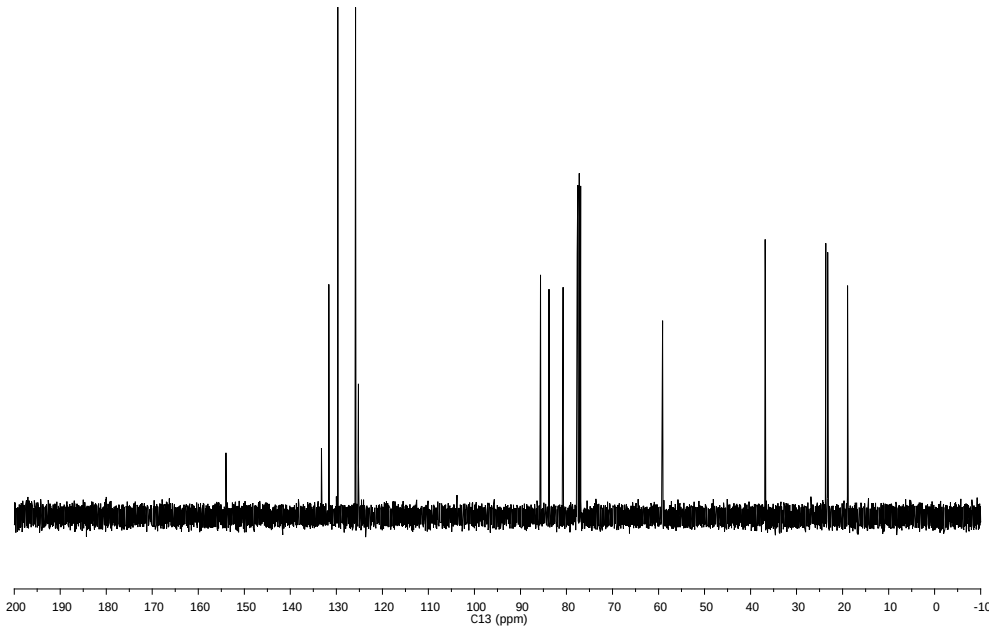
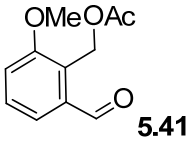
C13 (ppm)


PT
S
O
O
O
O
O

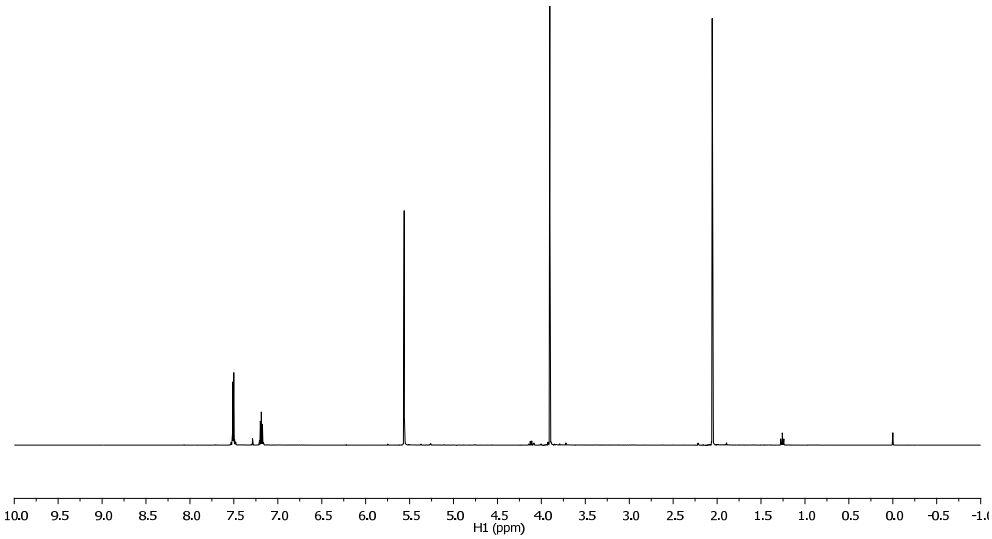
5.40


10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
H1 (ppm)


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
C13 (ppm)


OMe
OAc
O

5.41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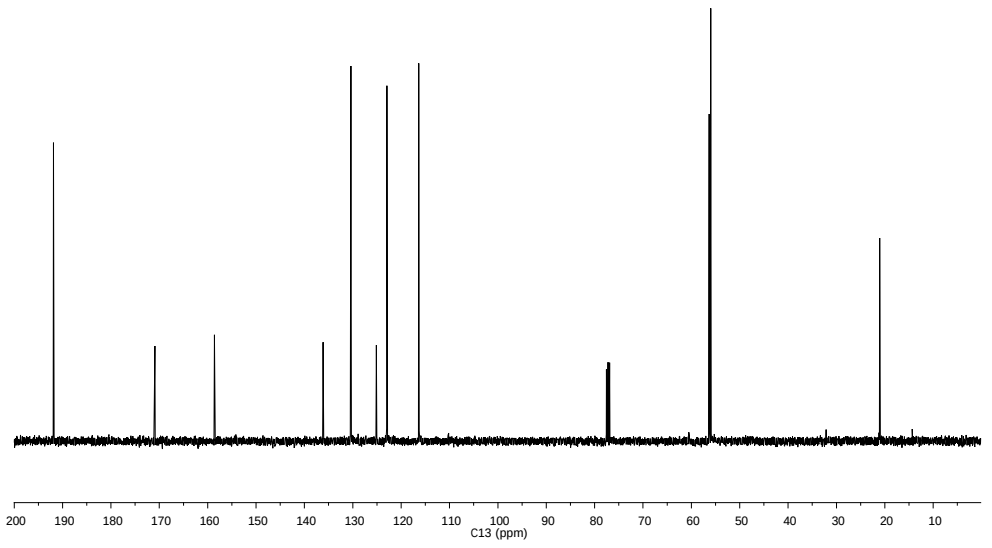
H1 (ppm)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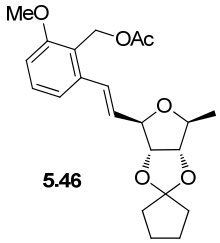
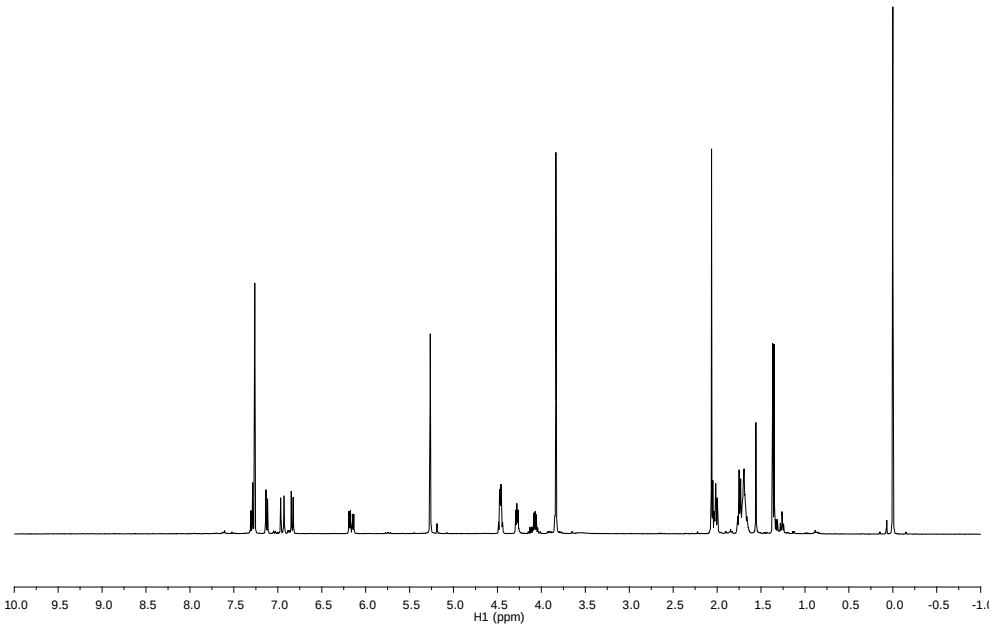
C13 (ppm)


MeO
OAc
O
O
O

5.46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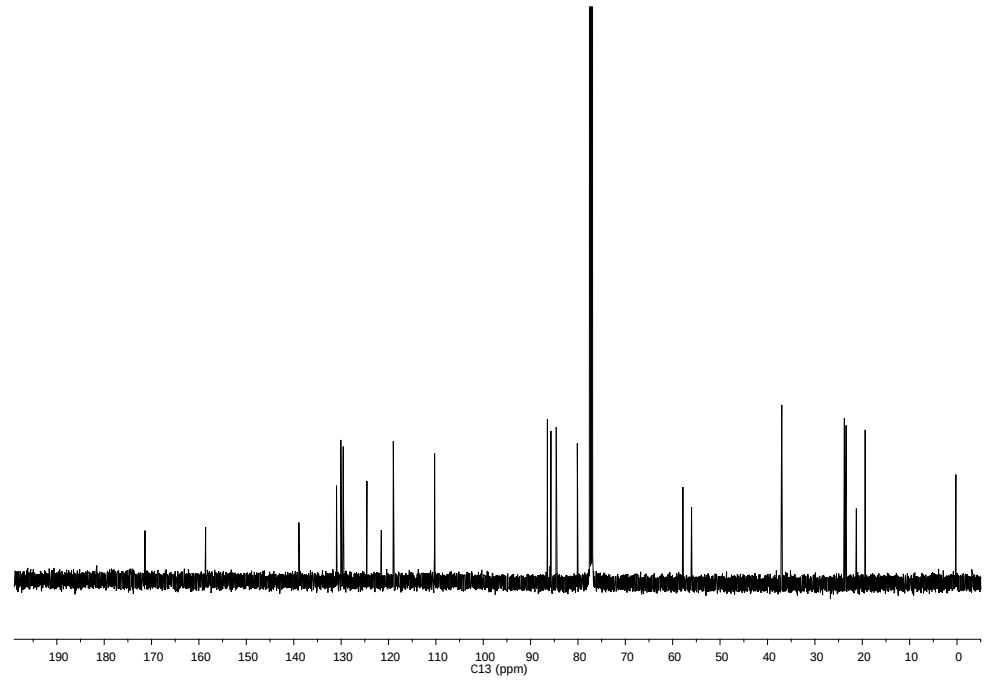
H1 (ppm)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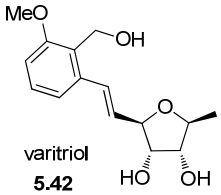
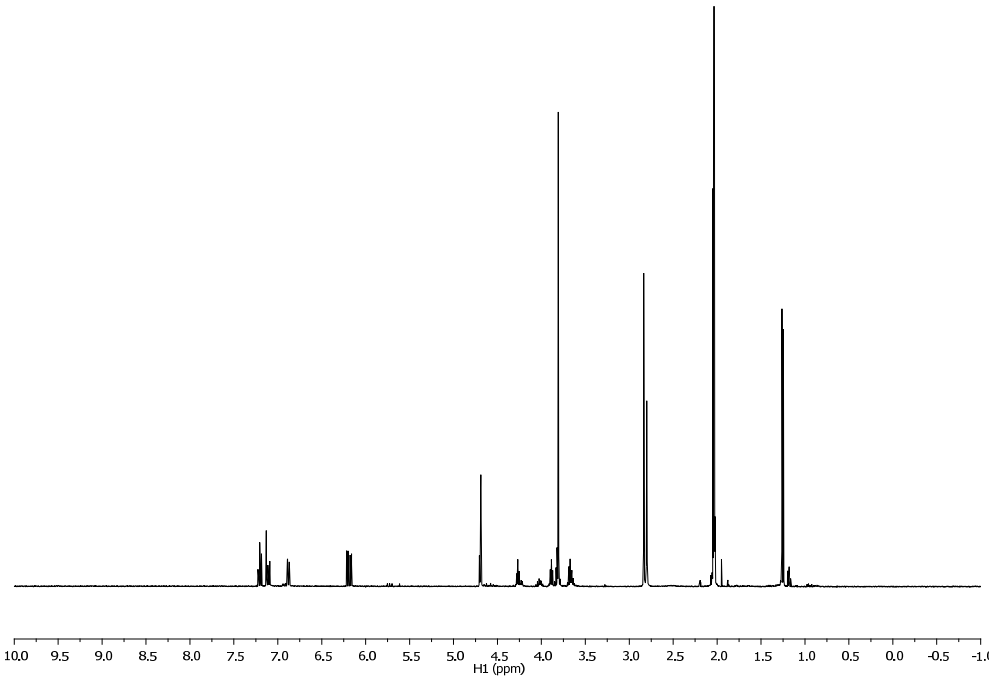
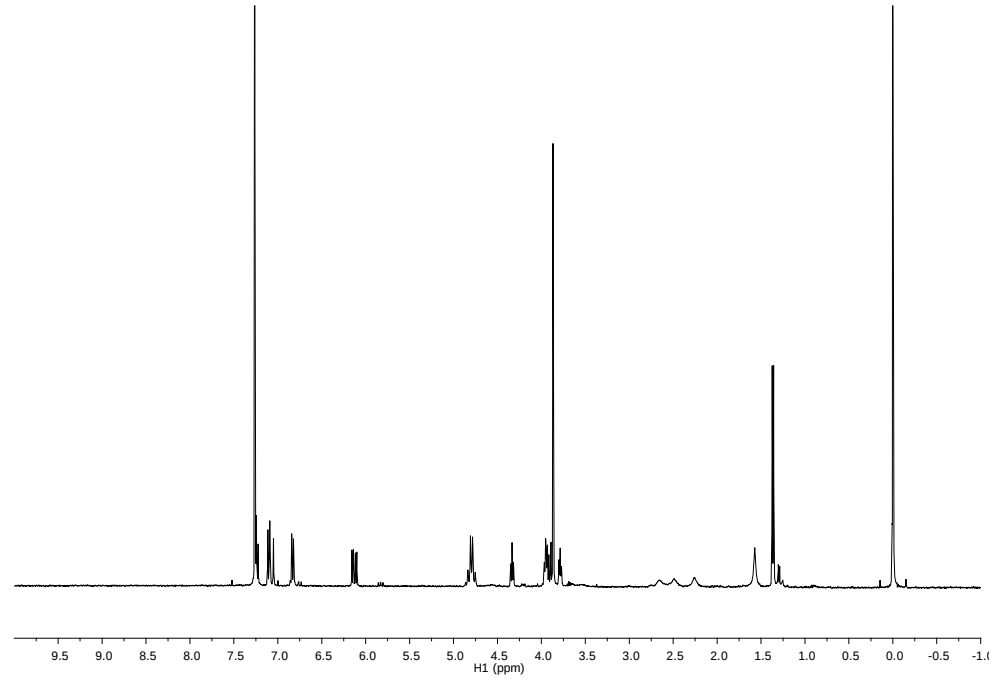
C13 (ppm)



varitriol

5.42



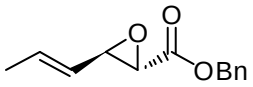


A5.3 Coordinates and Calculated Energies for Chapter 5

DFT calculations were performed with the program Gaussian03[1] by using the WebMO interface (WebMO, version 9.1.002p; www.webmo.net) for importing and constructing models. Transition states were verified by following the reaction coordinate forward and reverse (IRC).

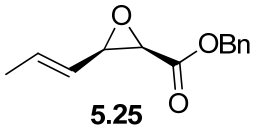
[1] Gaussian 03, Revision E.01, M. J. Frisch, G. W. Trucks, H. B. Schlegel, G. E. Scuseria, M. A. Robb, J. R. Cheeseman, J. A. Montgomery, Jr., T. Vreven, K. N. Kudin, J. C. Burant, J. M. Millam, S. S. Iyengar, J. Tomasi, V. Barone, B. Mennucci, M. Cossi, G. Scalmani, N. Rega, G. A. Petersson, H. Nakatsuji, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, M. Klene, X. Li, J. E. Knox, H. P. Hratchian, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, P. Y. Ayala, K. Morokuma, G. A. Voth, P. Salvador, J. J. Dannenberg, V. G. Zakrzewski, S. Dapprich, A. D. Daniels, M. C. Strain, O. Farkas, D. K. Malick, A. D. Rabuck, K. Raghavachari, J. B. Foresman, J. V. Ortiz, Q. Cui, A. G. Baboul, S. Clifford, J. Cioslowski, B. B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. L. Martin, D. J. Fox, T. Keith, M. A. Al-Laham, C. Y. Peng, A. Nanayakkara, M. Challacombe, P. M. W. Gill, B. Johnson, W. Chen, M. W. Wong, C. Gonzalez, and J. A. Pople, Gaussian, Inc., Wallingford CT, 2004.

Structure	Method	Basis Set	Corrected Energy (hartree)	Corrected Energy (kcal/mol)	Relative Energy (kcal/mol)
5.24	B3LYP	6-311+G(d,p)	-729.430	-459540.92	0.0
5.25	B3LYP	6-311+G(d,p)	-729.429	-459540.33	0.6
5.22	B3LYP	6-311+G(d,p)	-729.451	-459554.46	-13.5
5.26	B3LYP	6-311+G(d,p)	-729.452	-459554.83	-13.9



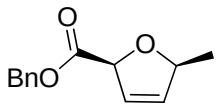
5.24

C	0.00000000	0.00000000	0.00000000
C	0.74557900	1.12625200	-0.59213800
C	1.39584300	2.03481500	0.13815900
C	2.16277600	3.19852600	-0.41042700
H	3.21007900	3.15910700	-0.09196200
H	2.13758200	3.22117400	-1.50206900
H	1.75774800	4.14579100	-0.03772400
H	1.38037200	1.93607500	1.22292100
H	0.75283400	1.18106100	-1.67872700
O	0.04079800	-1.25985100	-0.68265600
C	-1.20370000	-0.58269500	-0.65832900
C	-2.27509100	-1.19194800	0.21597500
O	-3.53354100	-0.69506200	0.09988800
C	-3.85085300	0.41343800	-0.78594000
C	-5.27058800	0.82781600	-0.51608900
C	-5.55230800	1.82204400	0.42446900
C	-6.86888900	2.18949800	0.69260400
C	-7.91754900	1.56334200	0.02071200
C	-7.64537100	0.57024800	-0.91919000
C	-6.32787500	0.20600700	-1.18590100
H	-6.11861000	-0.56983100	-1.91507200
H	-8.45798900	0.08091000	-1.44395400
H	-8.94270000	1.84902900	0.22764900
H	-7.07602900	2.96264700	1.42373300
H	-4.73784900	2.30826600	0.95161700
H	-3.73898700	0.08649700	-1.82357300
H	-3.16595400	1.24329500	-0.59418000
O	-2.05170100	-2.06180600	1.01091100
H	-1.50785500	-0.17151600	-1.61624300
H	0.04339400	-0.09727000	1.08318500



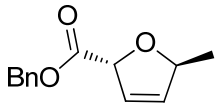
5.25

C	0.00000000	0.00000000	0.00000000
C	0.41257800	1.15207200	0.82416200
C	0.85994800	2.29163300	0.29177500
C	1.28960900	3.49648400	1.07101400
H	2.33137100	3.75251400	0.84913700
H	0.68762200	4.37170500	0.80282900
H	1.19767900	3.33402800	2.14675100
H	0.92866300	2.37067000	-0.79303700
H	0.34579300	1.02359100	1.90063700
O	0.30510800	-1.31283700	0.49427700
C	-1.06298800	-0.96459300	0.41283400
C	-1.80014700	-0.79400800	1.71919200
O	-3.12925900	-0.52287400	1.63469900
C	-3.77074700	-0.22585100	0.38028600
C	-5.12889200	0.38056500	0.64454500
C	-6.11053900	0.29928300	-0.34756800
C	-7.35617900	0.89382000	-0.16164300
C	-7.63660500	1.56812600	1.02590500
C	-6.66431700	1.64320700	2.02108200
C	-5.41462100	1.05406300	1.83360900
H	-4.66491200	1.10138400	2.61307800
H	-6.87820600	2.15865500	2.95070800
H	-8.60795900	2.02536600	1.17634400
H	-8.10915500	0.82149100	-0.93831500
H	-5.90393600	-0.23446700	-1.27049000
H	-3.88222400	-1.14461700	-0.20465500
H	-3.15254300	0.47563700	-0.19030900
O	-1.28335900	-0.88925800	2.79660900
H	-1.61191500	-1.47330500	-0.37694000
H	0.14420600	0.11192800	-1.07405300



5.22

C	0.00000000	0.00000000	0.00000000
C	0.70435600	-0.48239300	1.23866700
C	2.01861900	-0.50979900	1.05271000
C	2.33168900	-0.02820300	-0.34904900
O	1.07060500	0.15985700	-0.96116500
C	3.11881900	1.30384800	-0.30033800
O	4.47665700	1.23984200	-0.22923400
C	5.21338200	0.00976000	-0.31807200
C	6.68268400	0.28932000	-0.09285100
C	7.60702600	-0.71947000	-0.38434500
C	8.96627100	-0.51959000	-0.16097800
C	9.41798700	0.69685000	0.35103000
C	8.50137900	1.70560400	0.63573800
C	7.13789100	1.50574600	0.41638600
H	6.42710200	2.29336200	0.62891200
H	8.84495800	2.65625200	1.02805300
H	10.4766270	0.85651100	0.52134000
H	9.67214700	-1.30928000	-0.39256700
H	7.26462200	-1.66689500	-0.79059800
H	4.85562700	-0.69953000	0.43607400
H	5.06937200	-0.43846200	-1.30665600
O	2.58626600	2.37573400	-0.28280000
H	2.89067500	-0.76877500	-0.93157200
H	2.77257400	-0.79073900	1.77590400
H	0.18206800	-0.74917100	2.14844100
C	-0.77522600	1.30383200	0.17322100
H	-1.19861500	1.61319100	-0.78472400
H	-1.59615600	1.16606500	0.88417100
H	-0.11351900	2.09394700	0.53133400
H	-0.67133800	-0.77372900	-0.39551000



5.26

C	0.00000000	0.00000000	0.00000000
C	0.88248300	-1.08346200	0.55535400
C	0.19230600	-1.89655100	1.34428800
C	-1.24053600	-1.44544300	1.40973000
O	-1.28381100	-0.24006600	0.63085200
C	-2.21807700	-2.50123400	0.84637400
O	-3.53320500	-2.19745100	0.81017100
C	-4.06539500	-0.96331400	1.33236600
C	-5.53033000	-0.85934400	0.97472500
C	-6.22643700	0.29097700	1.36339100
C	-7.57767700	0.43646200	1.06447700
C	-8.25154400	-0.56824200	0.36928600
C	-7.56250100	-1.71341100	-0.02029300
C	-6.20760700	-1.86217700	0.28068500
H	-5.67389500	-2.75303700	-0.02274800
H	-8.07795300	-2.49901100	-0.56164300
H	-9.30387500	-0.45650900	0.13383400
H	-8.10376200	1.33347400	1.37163300
H	-5.70842200	1.07944700	1.90180100
H	-3.95018700	-0.96195700	2.42265100
H	-3.50799500	-0.12028900	0.92287300
O	-1.85334900	-3.58002800	0.45940100
H	-1.55040000	-1.21123600	2.43882000
H	0.55416600	-2.77279200	1.86217700
H	1.93262900	-1.16745300	0.30738500
C	0.45325000	1.42565800	0.29368200
H	-0.28860400	2.14051600	-0.06910300
H	1.40167800	1.63207500	-0.21115200
H	0.58808700	1.57311000	1.36784500
H	-0.12751500	-0.12370700	-1.08481500

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